(19) JAPANESE PATENT OFFICE (JP)

[12] OFFICIAL GAZETTE FOR KOKAI PATENT APPLICATIONS (A)

[11] JAPANESE PATENT APPLICATION LAID-OPEN PUBLICATION No. 07-101959

(43) Publication Date: April 18, 1995

(51) Int.Cl.[6]	Identification code	Japanese classification
C07D 519/00	311	
// A61K 31/40	ADZ	9454-4C
31/415		9454-4C
31/435		9454-4C
31/495		9454-4C
(C07D 519/00 487:00)		
(C07D 519/00 471:00 487:00)		

Examination Requested: Not yet made
Number of Claims: 1
(Total 55 pages)

(54) TITLE OF INVENTION: 1-METHYLCARBAPENEM DERIVATIVE

(21) Application Filing no.: 5-244299

(22) Application Filing date: September 30, 1993

(72) Inventor(s): Sadao OIDA
c/o Sankyo CO., Ltd. 2-58 Hiromachi 1-chome, Shinagawa-ku, Tokyo.
Teruo TANAKA
c/o Sankyo CO., Ltd. 2-58 Hiromachi 1-chome, Shinagawa-ku, Tokyo.
Toshiyuki KONOSU
c/o Sankyo CO., Ltd. 2-58 Hiromachi 1-chome, Shinagawa-ku, Tokyo.
Makoto MORI
c/o Sankyo CO., Ltd. 2-58 Hiromachi 1-chome, Shinagawa-ku, Tokyo.
Takeo MIYAOKA
c/o Sankyo CO., Ltd. 2-58 Hiromachi 1-chome, Shinagawa-ku, Tokyo.
Kazu TAJIMA
c/o Sankyo CO., Ltd. 2-58 Hiromachi 1-chome, Shinagawa-ku, Tokyo.

(71) Assignee(s): Kuraray Co., Ltd.
5-1 Nihonbashi-honcho 3-chome, Chuo-ku, Tokyo.

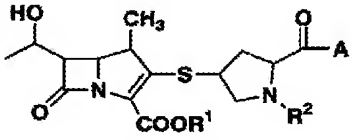
(74) Agent(s): Patent Attorney Akio OHNO (and two others)

(57) Abstract

(Amended)

Construction

1-methylcarbapenem derivative represented by general formula (1) and salts thereof



(1)

[wherein, R^1 denotes H, protecting group; R^2 denotes H, protecting group, alkyl, alkenyl, -C(=NR^3)R^4 (R^3 denotes H, protecting group; R^4 denotes H, alkyl, amino group), A denotes fused heterocycle (3,7-diazabicyclo[3,3,0] octane and the like].

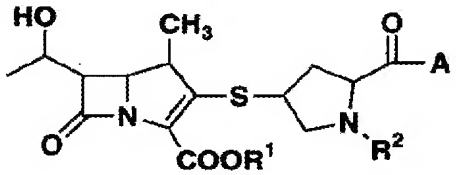
Effect

The compound of this invention has excellent antibacterial activity and is useful as antibacterial drug.

Patent Claims

Claim 1

1-methylcarbapenem derivative represented by general formula and salts thereof



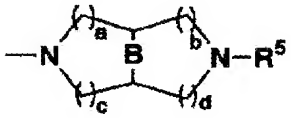
(1)

[wherein, R^1 denotes a hydrogen atom or protecting group,

R^2 denotes a hydrogen atom, protecting group, alkyl group, alkenyl group or -C(=NR^3)R^4 group (wherein, R^3 denotes a hydrogen atom or protecting group, and R^4 denotes a hydrogen atom, alkyl group or amino group),

A denotes a group selected from the following (2) to (12).

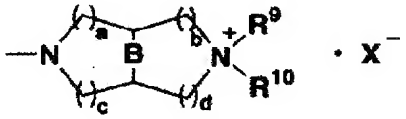
Formula (2)



(wherein, R^5 is a hydrogen atom, protecting group, optionally substituted alkyl group (wherein, the said substituent is selected from a hydroxy group, protected hydroxy group, carboxy group, protected

carboxy group, cyano group, alkoxy group, alkylsulfonyl group, -NHCOR^6 group (wherein, R^6 denotes hydrogen atom or alkyl group), -NR^{7}R^8 group (wherein, R^7 and R^8 are the same or different and denote a hydrogen atom, alkyl group or protecting group), -CONR^{7a}R^{8a} group (wherein, R^{7a} and R^{8a} denote a hydrogen atom or alkyl group) or -OCONR^{7a}R^{8a} group (wherein, R^{7a} and R^{8a} have the same aforesaid meanings)) or -C(=NR^3)R^4 group (wherein, R^3 and R^4 have the same aforesaid meanings), a, b, c and d each independently denote 0, 1, 2 or 3 (but excluding a=b=c=d=0), -B- denotes a single bond, double bond, methylene group, ethylene group or propylene group);

Formula (3)

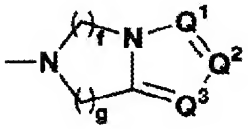


(wherein, R^9 and R^{10} which may be the same or different denote optionally substituted alkyl groups (wherein, the said substituent is selected from a hydroxy group, protected hydroxy group, carboxy group, protected carboxy group, cyano group, alkoxy group, alkylsulfonyl group, -NHCOR^6 group (wherein, R^6 has the same aforesaid meaning), -NR^{7}R^8 group (wherein, R^7 and R^8 have the same aforesaid meanings), -CONR^{7a}R^{8a} group (wherein, R^{7a} and R^{8a} have the same aforesaid meanings) or -OCONR^{7a}R^{8a} group (wherein, R^{7a} and R^{8a} denote hydrogen atom or alkyl group)),

X$^-$ denotes an anion,

a, b, c and d have the same aforesaid meaning and -B- have the same aforesaid meanings);

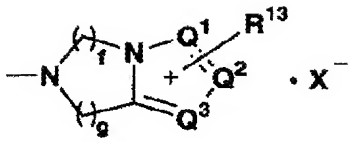
Formula (4)



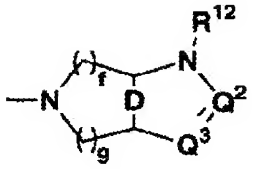
(wherein, Q^1, Q^2 and Q^3 each independently denote CR^{11} group (wherein, R^{11} is a hydrogen atom, amino group, optionally substituted alkyl group (wherein, the said substituent is selected from a hydroxy group, protected hydroxy group, carboxy group, protected carboxy group, cyano group, alkoxy group, alkylsulfonyl group, -NHCOR^6 group (wherein, R^6 has the same aforesaid meaning), -NR^{7}R^8 group (wherein, R^7 and R^8 have the same aforesaid meanings), -CONR^{7a}R^{8a} group (wherein, R^{7a} and R^{8a} have the same aforesaid meanings) or -OCONR^{7a}R^{8a} group (wherein, R^{7a} and R^{8a} have the same aforesaid meanings)) or nitrogen atom,

f and g each independently denote 0, 1, 2 or 3 (but excluding f=g=0));

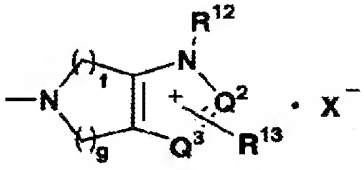
Formula (5)



(wherein, Q^1, Q^2 and Q^3 each independently denote CR^{11} group (wherein, R^{11} have the same aforesaid meanings) or nitrogen atom (at least one of Q^1, Q^2, Q^3 is nitrogen atom),
f and g each independently denote 0, 1, 2 or 3,
R^{13} is a group bonded to a nitrogen atom and denotes optionally substituted alkyl group (wherein, the said substituent is selected from a hydroxy group, protected hydroxy group, carboxy group, protected carboxy group, cyano group, alkoxy group, alkylsulfonyl group, $-NHCOR^6$ group (wherein, R^6 has the same aforesaid meaning), $-NR^7R^8$ group (wherein, R^7 and R^8 have the same aforesaid meanings), $-CONR^{7a}R^{8a}$ group (wherein, R^{7a} and R^{8a} have the same aforesaid meanings) or $-OCONR^{7a}R^{8a}$ group (wherein, R^{7a} and R^{8a} have the same aforesaid meanings)) and
X^- denotes an anion);
Formula (6)



(wherein, Q^2 and Q^3 each independently denote CR^{11} group (wherein, R^{11} has the same aforesaid definition) or nitrogen atom,
R^{12} denotes a hydrogen atom, alkyl group or protecting group,
f and g have the same aforesaid definitions and
-D- denotes a single bond or double bond);
Formula (7)

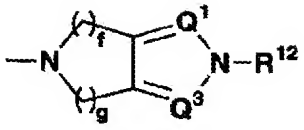


(wherein, Q^2 and Q^3 each independently denote CR^{11} group (wherein, R^{11} has the same aforesaid definition) or nitrogen atom,
R^{12} has the same aforesaid definition,
R^{13} has the same aforesaid definition

f and g have the same aforesaid definitions and

X^- denotes an anion);

Formula (8)

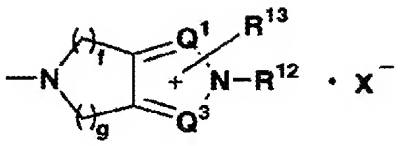


(wherein, Q^1 and Q^3 each independently denote CR^{11} group (wherein, R^{11} has the same aforesaid definition) or nitrogen atom,

R^{12} has the same aforesaid definition and

f and g have the same aforesaid meanings);

Formula (9)



(wherein, Q^1 and Q^3 each independently denote CR^{11} group (wherein, R^{11} has the same aforesaid meanings) or nitrogen atom (at least one of Q^1, Q^3 is a nitrogen atom to which R^{13} is bonded),

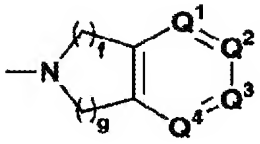
R^{12} has the same aforesaid definition,

R^{13} has the same aforesaid definition,

f and g have the same aforesaid definitions, and

X^- denotes an anion);

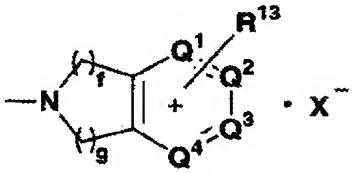
Formula (10)



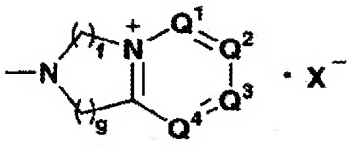
(wherein, Q^1, Q^2, Q^3 and Q^4 each independently denote CR^{11} group (wherein, R^{11} has the same aforesaid definition) or nitrogen atom

and f and g have the same aforesaid meanings);

Formula (11)



(wherein, Q^1, Q^2, Q^3 and Q^4 each independently denote CR^{11} group (wherein, R^{11} has the same aforesaid meanings) or nitrogen atom (at least one of Q^1, Q^2, Q^3, Q^4 is nitrogen atom to which R^{13} is bonded),
R^{13} has the same aforesaid definition,
f and g have the same aforesaid definitions, and
X^- denotes an anion);
Formula (12)



(wherein, Q^1, Q^2, Q^3 and Q^4 each independently denote CR^{11} group (wherein, R^{11} has the same aforesaid definition) or nitrogen atom,
f and g have the same aforesaid definitions, and
X^- denotes an anion);].

Detailed Description of the Invention

(0001)

Sphere of Application in Industry

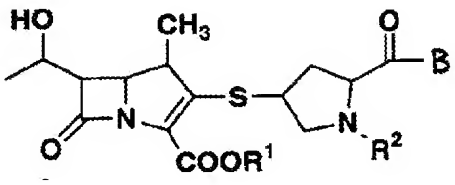
This invention relates to the following, namely, a novel 1-methylcarbapenem derivative having an excellent antibacterial action.

(0002)

Technology of the Prior Art

In Kokai 4-211083, there is described a compound wherein B is monocyclic heterocycle in the following formula.

(0003)



(0004)

Problems to be Overcome by this Invention

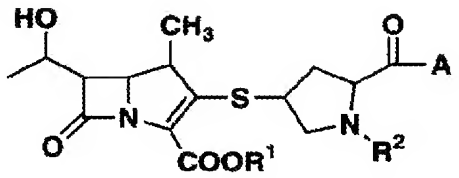
These inventors carried out assiduous investigation over a long period of time into the synthesis of derivatives having a superior antibacterial activity and pharmacological activity , and as a result, discovered novel 1-carbapenem derivatives having excellent bacteria activity and little toxicity. This invention was completed as a result of this discovery.

(0005)

Means to Overcome these Problems

Novel 1-methylcarbapenem derivative of this invention has general formula (1).

(0006) (0007)



(1)

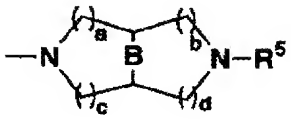
(0008)

In the aforesaid formula (1), R^1 denotes a hydrogen atom or protecting group,
R^2 denotes a hydrogen atom, protecting group, alkyl group, alkenyl group or $-C(=NR^3)R^4$ group (wherein, R^3 denotes a hydrogen atom or protecting group, and R^4 denotes a hydrogen atom, alkyl group or amino group), and A denotes a group selected from the following (2) to (12).

(0009)

Formula (2)

(0010)



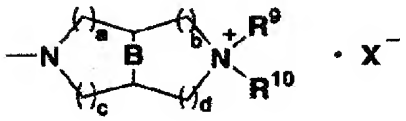
(0011)

(wherein, R^5 is a hydrogen atom, protecting group, optionally substituted alkyl group (wherein, the said substituent is selected from a hydroxy group, protected hydroxy group, carboxy group, protected carboxy group, cyano group, alkoxy group, alkylsulfonyl group, $-NHCOR^6$ group (wherein, R^6 denotes hydrogen atom or alkyl group), $-NR^7R^8$ group (wherein, R^7 and R^8 are the same or different and denote a hydrogen atom, alkyl group or protecting group), $-CONR^{7a}R^{8a}$ group (wherein, R^{7a} and R^{8a} denote a hydrogen atom or alkyl group) or $-OCONR^{7a}R^{8a}$ group (wherein, R^{7a} and R^{8a} have the same

aforesaid meanings)) or -C(=NR^3)R^4 group (wherein, R^3 and R^4 have the same aforesaid meanings), a, b, c and d each independently denote 0, 1, 2 or 3 (but excluding a=b=c=d=0), -B- denotes a single bond, double bond, methylene group, ethylene group or propylene group);

Formula (3)

(0012)

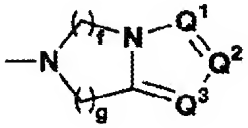


(0013)

(wherein, R^9 and R^{10} which may be the same or different denote optionally substituted alkyl group (wherein, the said substituent is selected from a hydroxy group, protected hydroxy group, carboxy group, protected carboxy group, cyano group, alkoxy group, alkylsulfonyl group, -NHCOR^6 group (wherein, R^6 has the same aforesaid meaning), -NR^{7}R^8 group (wherein, R^7 and R^8 have the same aforesaid meanings), -CONR^{7a}R^{8a} group (wherein, R^{7a} and R^{8a} have the same aforesaid meanings) or -OCONR^{7a}R^{8a} group (wherein, R^{7a} and R^{8a} denote hydrogen atom or alkyl group)), X$^-$ denotes an anion, a, b, c and d have the same aforesaid meaning and -B- have the same aforesaid meanings);

Formula (4)

(0014)

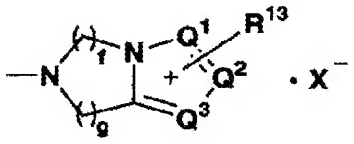


(0015)

(wherein, Q^1, Q^2 and Q^3 each independently denote CR^{11} group (wherein, R^{11} is a hydrogen atom, amino group, optionally substituted alkyl group (wherein, the said substituent is selected from a hydroxy group, protected hydroxy group, carboxy group, protected carboxy group, cyano group, alkoxy group, alkylsulfonyl group, -NHCOR^6 group (wherein, R^6 has the same aforesaid meaning), -NR^{7}R^8 group (wherein, R^7 and R^8 have the same aforesaid meanings), -CONR^{7a}R^{8a} group (wherein, R^{7a} and R^{8a} have the same aforesaid meanings) or -OCONR^{7a}R^{8a} group (wherein, R^{7a} and R^{8a} have the same aforesaid meanings)) or nitrogen atom, f and g each independently denote 0, 1, 2 or 3 (but excluding f=g=0));

Formula (5)

(0016)

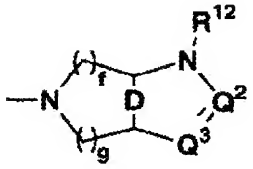


(0017)

(wherein, Q^1, Q^2 and Q^3 each independently denote CR^{11} group (wherein, R^{11} have the same aforesaid meanings) or nitrogen atom (at least one of Q^1, Q^2, Q^3 is nitrogen atom), f and g each independently denote 0, 1, 2 or 3, R^{13} is a group bonded to nitrogen atom and denotes optionally substituted alkyl group (wherein, the said substituent is selected from a hydroxy group, protected hydroxy group, carboxy group, protected carboxy group, cyano group, alkoxy group, alkylsulfonyl group, -NHCOR^6 group (wherein, R^6 has the same aforesaid meaning), -NR^{7}R^8 group (wherein, R^7 and R^8 have the same aforesaid meanings), -CONR^{7a}R^{8a} group (wherein, R^{7a} and R^{8a} have the same aforesaid meanings) or -OCONR^{7a}R^{8a} group (wherein, R^{7a} and R^{8a} have the same aforesaid meanings)) and X^- denotes an anion);

Formula (6)

(0018)

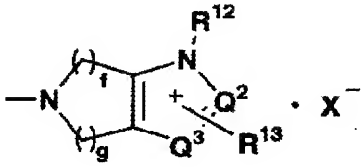


(0019)

(wherein, Q^2 and Q^3 each independently denote CR^{11} group (wherein, R^{11} has the same aforesaid definition) or nitrogen atom, R^{12} denotes a hydrogen atom, alkyl group or protecting group, f and g have the same aforesaid definitions and -D- denotes a single bond or double bond);

Formula (7)

(0020)

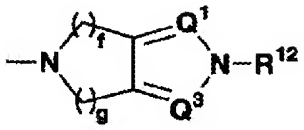


(0021)

(wherein, Q^2 and Q^3 each independently denote CR^{11} group (wherein, R^{11} has the same aforesaid definition) or nitrogen atom, R^{12} has the same aforesaid definition, R^{13} has the same aforesaid definition, f and g have the same aforesaid definitions and X^- denotes an anion);

Formula (8)

(0022)

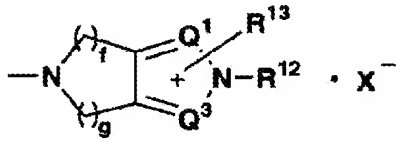


(0023)

(wherein, Q^1 and Q^3 each independently denote CR^{11} group (wherein, R^{11} has the same aforesaid definition) or nitrogen atom, R^{12} has the same aforesaid definition and f and g have the same aforesaid meanings);

Formula (9)

(0024)

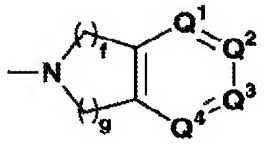


(0025)

(wherein, Q^1 and Q^3 each independently denote CR^{11} group (wherein, R^{11} has the same aforesaid meanings) or nitrogen atom (at least one of Q^1, Q^3 is a nitrogen atom to which R^{13} is bonded), R^{12} has the same aforesaid definition, R^{13} has the same aforesaid definition, f and g have the same aforesaid definitions, and X^- denotes an anion);

Formula (10)

(0026)

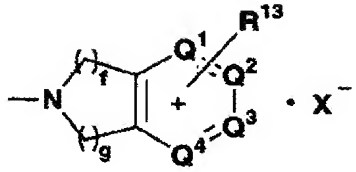


(0027)

(wherein, Q^1, Q^2, Q^3 and Q^4 each independently denote CR^{11} group (wherein, R^{11} has the same aforesaid definition) or nitrogen atom and f and g have the same aforesaid meanings);

Formula (11)

(0028)

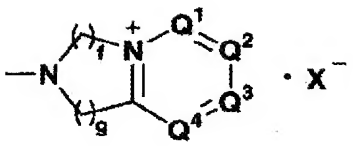


(0029)

(wherein, Q^1, Q^2, Q^3 and Q^4 each independently denote CR^{11} group (wherein, R^{11} has the same aforesaid meanings) or nitrogen atom (at least one of Q^1, Q^2, Q^3, Q^4 is nitrogen atom in which R^{13} is bonded), R^{13} has the same aforesaid definition, f and g have the same aforesaid definitions, and X^- denotes an anion);

Formula (12)

(0030)



(0031)

(wherein, Q^1, Q^2, Q^3 and Q^4 each independently denote CR^{11} group (wherein, R^{11} has the same aforesaid definition) or nitrogen atom, f and g have the same aforesaid definitions, and X^- denotes an anion).

(0032)

Protecting group of carboxy group of R^1 in the aforesaid formula (1) denotes a protecting group in the reaction and a protecting group for prodrug formation for administration to a living body, and for example, protecting group in the reaction as exemplified by lower alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, pentyl, hexyl and the like; halogeno lower alkyl group such as 2,2,2-trichloroethyl, 2-bromoethyl, 2-chloroethyl, 2-fluoroethyl, 2,2-dibromoethyl and the like; aralkyl group for example lower alkyl group substituted by 1 to 3 aryl groups such as benzyl, phenethyl, 3-phenylpropyl, α-naphthylmethyl, β-naphthylmethyl, diphenylmethyl, triphenylmethyl, α-naphthyl diphenylmethyl, 9-anthrylmethyl and the like, lower alkyl group substituted by 1 to 3 aryl groups in which aryl ring is substituted by lower alkyl, lower alkoxy, nitro, halogen or cyano group, such as 4-methylbenzyl, 2,4,6-trimethyl benzyl, 3,4,5-trimethyl benzyl, 4-methoxybenzyl, 4-methoxyphenyl diphenylmethyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-bromobenzyl, 4-cyanobenzyl, 4-cyanobenzyl diphenylmethyl, bis(2-nitrophenyl) methyl, piperonyl and the like: and protecting group of carboxy group which is readily hydrolysed in vivo for prodrug formation for administration to living body as exemplified by alkoxymethyl group for example lower alkoxymethyl group such as methoxymethyl, 1,1-dimethyl-1-methoxymethyl, ethoxymethyl, n-propoxymethyl, isopropoxy methyl, n-butoxymethyl, t-butoxymethyl and the like, lower alkoxylated lower alkoxymethyl group such as 2-methoxyethoxy methyl and the like, halogenated lower alkoxymethyl such as 2,2,2-trichloroethoxy methyl, bis (2-chloroethoxy) methyl and the like; substituted ethyl group for example lower alkoxylated ethyl group such as 1-ethoxyethyl, 1-methyl-1-methoxyethyl, 1-(isopropoxy) ethyl and the like, halogenated ethyl group such as 2,2,2-trichloroethyl and the like, arylselenylated ethyl group such as 2-(phenylselenyl) ethyl and the like; aliphatic acyloxymethyl group such as acetoxymethyl, propionyloxy methyl, butyryl oxymethyl, pivaloyloxymethyl and the like; 1-lower alkoxycarbonyloxy ethyl group such as 1-methoxycarbonyloxy ethyl, 1-ethoxycarbonyloxy ethyl, 1-propoxy carbonyloxy ethyl, 1-isopropoxy carbonyloxy ethyl, 1-butoxycarbonyloxy ethyl, 1-isobutoxycarbonyloxy ethyl, 1-cyclohexyloxy carbonyloxy ethyl and the like; cyclohexyl oxycarbonyloxy (cyclohexyl) methyl;

phthalidyl group; (2-oxo-5-methyl-1,3-dioxolen-4-yl) methyl group may be proposed, and 4-nitrobenzyl, pivaloyloxymethyl, (2-oxo-5-methyl-1,3-dioxolen-4-yl) methyl group are preferred.

(0033)

As protecting group of the secondary amino group of R^2 in the aforesaid formula (1), any group as long it is a group generally used as protecting group of amino group can be used without limitation in particular, but preferably for example aliphatic acyl group such as alkyl carbonyl group such as formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, octanoyl, lauroyl, palmitoyl, stearoyl and the like, halogeno lower alkyl carbonyl group such as chloroacetyl, dicholroacetyl, trichloroacetyl, trifluoroacetyl and the like, lower alkoxy lower alkyl carbonyl group such as methoxyacetyl and the like, unsaturated alkyl carbonyl group such as (E)-2-methyl-2-butenoyl and the like; for example aromatic acyl group such as aryl carbonyl group such as benzoyl, α-naphthoyl, β-naphthoyl and the like, halogeno aryl carbonyl group such as 2-bromobenzoyl, 4-chlorobenzoyl and the like, lower alkoxylated aryl carbonyl group such as 2,4,6-trimethylbenzoyl, 4-toluoyl and the like, lower alkoxylated aryl carbonyl group such as 4-anisoyl and the like, nitrated aryl carbonyl group such as 4-nitrobenzoyl, 2-nitrobenzoyl and the like, lower alkoxycarbonylated aryl carbonyl group such as 2-(methoxycarbonyl) benzoyl and the like, arylated aryl carbonyl group such as 4-phenylbenzoyl and the like; for example alkoxycarbonyl group such as lower alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, isobutoxycarbonyl and the like, lower alkoxycarbonyl group substituted by halogen or tri-lower alkyl silyl group, such as 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilyl ethoxycarbonyl and the like, aralkyloxycarbonyl group such as benzyloxycarbonyl, 4-nitrobenzyloxy carbonyl, 4-methoxybenzyloxy carbonyl and the like, alkenyloxycarbonyl group such as or vinyl oxycarbonyl, allyl oxycarbonyl and the like may be proposed, but 4-nitrobenzyl oxycarbonyl and allyl oxycarbonyl group are preferred.

(0034)

As alkyl group of R^2 in the aforesaid formula (1), alkyl group of carbon number 1 to 6 may be proposed such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl, n-pentyl, isopentyl, 2-methylbutyl, neopentyl, 1-ethyl propyl, n-hexyl, 4-methyl pentyl, 3-methyl pentyl, 2-methyl pentyl, 1-methyl pentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl, 2-ethyl butyl or the like, but methyl and ethyl group are preferred.

(0035)

Moreover alkyl group of R^2 includes substituted alkyl group, and preferable substituent is hydroxy group, cyano group, fluorine atom, and moreover, as whole substituted alkyl group, preferably it is 2-

fluoroethyl or 2-hydroxyethyl group.

(0036)

As alkenyl group of R^2 in the aforesaid formula (1), straight or branched chain alkenyl group of carbon number 3 to 6 may be proposed such as 2-propenyl, 1-methyl-2-propenyl, 2-methyl-2-propenyl, 2-ethyl-2-propenyl, 2-butenyl, 1-methyl-2-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 1-ethyl-2-butenyl, 3-butenyl, 1-methyl-3-butenyl, 2-methyl-3-butenyl, 1-ethyl-3-butenyl, 2-pentenyl, 1-methyl-2-pentenyl, 2-methyl-2-pentenyl, 3-pentenyl, 1-methyl-3-pentenyl, 2-methyl-3-pentenyl, 4-pentenyl, 1-methyl-4-pentenyl, 2-methyl-4-pentenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl or the like, and 2-propenyl and 1-methyl-2-propenyl group are preferred.

(0037)

As protecting group of imino group of "R^3" of -C(=NR^3)R^4 group of R^2 in the aforesaid formula (1) and -C(=NR^3)R^4 group of R^5 in the aforesaid formula (2), the same groups as for the aforesaid "protecting group of the secondary amino group of R^2" may be proposed, and allyloxycarbonyl and 4-nitrobenzyl oxycarbonyl group are preferred.

(0038)

As alkyl group of "R^4" of -C(=NR^3)R^4 group of the aforesaid formula (1) and -C(=NR^3)R^4 group of R^5 of the aforesaid formulae (2), and alkyl group of R^7, $R^{7(sic?)}$, R^8 and $R^{8(sic?)}$ of "-NR^7 R^8 group", "-CON$R^{7a}R^{8a}$ group" and "-OCON$R^{7a}R^{8a}$ group" which are substituents of optionally substituted alkyl group of R^5, R^9 and R^{10} of the aforesaid (2) to (12), the same groups as the alkyl groups of the said R^2 may be proposed and methyl group and ethyl group are preferred.

(0039)

As optionally substituted alkyl group of R^5 in the aforesaid formula (2) and R^9 and R^{10} in aforesaid formula (3), methyl, cyanomethyl, 2-hydroxyethyl and carbamoylmethyl group are preferred.

(0040)

As protecting group of R^5 in the aforesaid formula (2), the same groups as in the aforesaid "protecting group of the secondary amino group of R^2" may be proposed and allyloxycarbonyl and 4-nitrobenzyl oxycarbonyl group are preferred.

(0041)

Moreover the protecting group of the "protected hydroxy group" which is substituent of the optionally

substituted alkyl group of R^5, R^9 and R^{10} denotes a protecting group in the reaction and a protecting group for prodrug formation for administration to a living body, and for example, protecting groups in the reaction as exemplified by for example aliphatic acyl groups such as alkyl carbonyl group such as formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, octanoyl, lauroyl, myristoyl, tri decanoyl, palmitoyl, stearoyl and the like, halogeno lower alkyl carbonyl group such as chloroacetyl, dicholroacetyl, trichloroacetyl, trifluoroacetyl and the like, lower alkoxy lower alkyl carbonyl group such as methoxyacetyl and the like, unsaturated alkyl carbonyl group such as (E)-2-methyl-2-butenoyl and the like; for example aromatic acyl group such as aryl carbonyl group such as benzoyl, α-naphthoyl, β-naphthoyl and the like, halogeno aryl carbonyl group such as 2-bromobenzoyl, 4-chlorobenzoyl and the like, lower alkoxylated aryl carbonyl group such as 2,4,6-trimethylbenzoyl, 4-toluoyl and the like, lower alkoxylated aryl carbonyl group such as 4-anisoyl and the like, nitrated aryl carbonyl group such as 4-nitrobenzoyl, 2-nitrobenzoyl and the like, lower alkoxycarbonylated aryl carbonyl group such as 2-(methoxycarbonyl) benzoyl and the like, arylated aryl carbonyl group such as 4-phenylbenzoyl and the like; for example tetrahydropyranyl or tetrahydrothiopyranyl group such as tetrahydropyran-2-yl, 3-bromo tetrahydropyran-2-yl, 4-methoxy tetrahydropyran-4-yl, tetrahydrothiopyran-2-yl, 4-methoxy tetrahydrothiopyran-4-yl and the like; tetrahydrofuranyl or tetrahydrothiofuranyl group such as tetrahydrofuran-2-yl, tetrahydrothiofuran-2-yl and the like; for example silyl group such as tri-lower alkyl silyl group such as trimethylsilyl, triethylsilyl, isopropyl dimethylsilyl, t-butyldimethylsilyl, methyl diisopropyl silyl, methyl di-t-butylsilyl, triisopropylsilyl and the like, tri-lower alkyl silyl group substituted by 1 to 2 aryl groups such as diphenylmethyl silyl, diphenyl butyl silyl, diphenyl isopropyl silyl, phenyl diisopropyl silyl and the like; for example alkoxymethyl group for example lower alkoxymethyl group such as methoxymethyl, 1,1-dimethyl-1-methoxymethyl, ethoxymethyl, n-propoxymethyl, isopropoxy methyl, butoxymethyl, t-butoxymethyl and the like, lower alkoxylated lower alkoxymethyl group such as 2-methoxyethoxy methyl and the like, halogeno lower alkoxymethyl such as 2,2,2-trichloroethoxy methyl, bis (2-chloroethoxy) methyl and the like; for example substituted ethyl group such as lower alkoxylated ethyl group such as 1-ethoxyethyl, 1-(isopropoxy) ethyl and the like, halogenated ethyl group such as, 2,2,2-trichloroethyl and the like; for example aralkyl group for example lower alkyl group substituted by 1 to 3 aryl groups such as benzyl, α-naphthylmethyl, β-naphthylmethyl, diphenylmethyl, triphenylmethyl, α-naphthyl diphenylmethyl, 9-anthrylmethyl and the like, lower alkyl group substituted by 1 to 3 aryl groups in which aryl ring is substituted by lower alkyl, lower alkoxy, halogen or cyano group such as 4-methylbenzyl, 2,4,6-trimethyl benzyl, 3,4,5-trimethyl benzyl, 4-methoxybenzyl, 4-methoxyphenyl diphenylmethyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-bromobenzyl, 4-cyanobenzyl, methyl, piperonyl and the like; for example alkoxycarbonyl group such as lower alkoxycarbonyl group such as methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, isobutoxycarbonyl and the like, lower alkoxycarbonyl group

substituted by halogen or tri-lower alkyl silyl group, such as 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilyl ethoxycarbonyl and the like; for examplealkenyl oxycarbonyl group such as vinyl oxycarbonyl, allyl oxycarbonyl and the like; for example aralkyl oxycarbonyl group in which aryl ring is optionally substituted by 1-2 lower alkoxy or nitro groups such as benzyl oxycarbonyl, 4-methoxybenzyl oxycarbonyl, 3,4-dimethoxybenzyl oxycarbonyl, 2-nitrobenzyl oxycarbonyl, 4-nitrobenzyl oxycarbonyl and the like: and protecting group which is readily hydrolysed in vivo for prodrug formation for administration to living body such as pivaloyloxymethyl oxycarbonyl and the like may be proposed, but wherein allyloxycarbonyl and 4-nitrobenzyl oxycarbonyl group are preferred.

(0042)

Moreover as the protecting group of the "protected carboxy group" which is substituent of the optionally substituted alkyl group of R^5, R^9 and R^{10}, the same groups as for the protecting groups of the carboxy group of the said R^1 may be proposed, and allyl and 4-nitrobenzyl group are preferred.

(0043)

Moreover as the alkoxy group which is substituent of the optionally substituted alkyl group of R^5, R^9 and R^{10}, straight or branched chain alkoxy group of carbon number 1 to 6 may be proposed such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, s-butoxy, t-butoxy, n-pentoxy, isopentoxy, 2-methyl butoxy, neopentoxy, n-hexyloxy, 4-methyl pentoxy, 3-methyl pentoxy, 2-methyl pentoxy, 3,3-dimethyl butoxy, 2,2-dimethyl butoxy, 1,1-dimethyl butoxy, 1,2-dimethyl butoxy, 1,3-dimethyl butoxy, and 2,3-dimethyl butoxy, and methoxy and ethoxy group are preferred.

(0044)

Moreover as alkylsulfonyl group which is substituent of the optionally substituted alkyl group of R^5, R^9 and R^{10}, straight or branched chain alkylsulfonyl group of carbon number 1 to 6 may be proposed such as methanesulphonyl, ethane sulfonyl, n-propane sulfonyl, isopropane sulfonyl, n-butane sulfonyl, isobutane sulfonyl, s-butane sulfonyl, t-butane sulfonyl, n-pentane sulfonyl, isopentane sulfonyl, 2-methylbutane sulfonyl, neopentane sulfonyl, n-hexane sulfonyl, 4-methylpentane sulfonyl, 3-methylpentane sulfonyl, 2-methylpentane sulfonyl, 3,3-dimethylbutane sulfonyl, 2,2-dimethylbutane sulfonyl, 1,1-dimethylbutane sulfonyl, 1,2-dimethylbutane sulfonyl, 1,3-dimethylbutane sulfonyl, 2,3-dimethylbutane sulfonyl, may be proposed, and methanesulphonyl and ethane sulphonyl group are preferred.

(0045)

Moreover as protecting group of R^7 and R^8 of $-NR^7R^8$ group which is substituent of the optionally

substituted alkyl group of R^5, R^9 and R^{10}, the same groups as for the aforesaid "protecting group of the secondary amino group of R^2" may be proposed, and allyl oxycarbonyl and 4-nitrobenzyl oxycarbonyl group are preferred.

(0046)

The ideal combination among the combinations of a, b, c and d in the aforesaid formulae (2) and (3) is (a, b, c, d)= (1, 1, 1, 1) (1, 2, 1, 0) (0, 1, 2, 1) (0, 1, 1, 0) (1, 3, 1, 0) and (0, 1, 0, 1).

(0047)

Among -B- in the aforesaid formulae (2) and (3), single bond, double bond and methylene group are preferred.

(0048)

As X^- of the aforesaid formulae (3), (5), (7), (9), (11) and (12), for example inorganic anion such as Cl^-, Br^-, $CF_3SO_3^-$, $CH_3SO_3^-$, NO_3^-, 1/2 SO_4^{2-} or the like may be proposed, and Cl^-, 1/2 SO_4^{2-} are preferred.

(0049)

As substituent of the optionally substituted alkyl group of CR^{11} group of Q^1, Q^2, Q^3 and Q^4 in the aforesaid formulae (4) to (12), the same group as proposed for aforesaid R^5 may be proposed, and preferably as regards protected hydroxy group, it is allyloxycarbonyl oxy, 4-nitrobenzyl oxycarbonyl group, as regards protected carboxy group, it is 4-nitrobenzyl, as regards alkoxy group, it is methoxy group, as rgards alkylsulfonyl group, it is methanesulphonyl group, as regards -$NHCOR^6$ group, it is formyl amino, acetylamino group, as regards -NR^7 R^8 group, it is amino, methylamino, dimethylamino group, as regards -$CONR^{7a}R^{8a}$ group, it is carbamoyl, N-methylcarbamoyl group, and as regards -$OCONR^{7a}R^{8a}$ group, it is carbamoyloxy, N-methylcarbamoyloxy group.

(0050)

Among the combination of f and g in the aforesaid formulae (4) to (12), ideal combinations are (f, g)=(2, 1), (1, 1) and (2, 0).

(0051)

As substituent of the optionally substituted alkyl group of R^{13} in the aforesaid formulae (5), (7), (9) and (11), the same groups as proposed for aforesaid R^5 may be proposed, and preferably as regards protected hydroxy group, it is 4-nitrobenzyl oxycarbonyl oxy group, as regards protected carboxy group,

it is 4-nitrobenzyl oxycarbonyl group, as regards alkoxy group, it is methoxy group, as regards alkylsulfonyl group, it is methanesulphonyl group, as regards -NHCOR^6 group, it is acetylamino group, as regards -NR^7 R^8 group, it vis amino, monomethyl amino group, as regards -CONR^{7a}R^{8a} group, it is carbamoyl group, as regards -OCONR^{7a}R^{8a} group, it is carbamoyloxy group. As alkyl group of R^{12} in the aforesaid formulae (6), (7), (8) and (9), the same groups as alkyl group of the said R^2 may be proposed and preferably methyl, ethyl group.

(0052)

As protecting group of R^{12} in the aforesaid formulae (6), (7), (8) and (9), the same groups as protecting group of the secondary amino group of the said R^2 may be proposed, and 4-nitrobenzyl oxycarbonyl group is preferred.

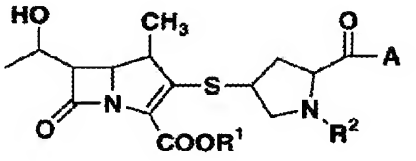
(0053)

Among -D- in the aforesaid formula (6), single bond and double bond are preferred. An ideal formulae among formulae (2) to (12) wherefrom A can be selected in the aforesaid formula (1) are (2), (3), (4), (5), (6) and (12).

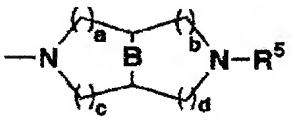
(0054)

Among the compounds of this invention, ideal compounds are exemplified below, however, this invention is not restricted to these.

(0055)



(1)



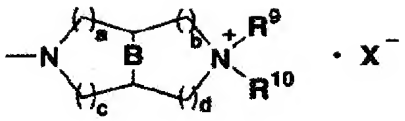
(0056)

Table 1

No.	R^1	R^2	Form	a b c d	R^5	-B-
1	H	H	(2)	1 1 1 1	CH_3	$-CH_2-$
2	H	CH_3	(2)	1 1 1 1	CH_3	$-CH_2-$
3	H	CH_3	(2)	1 1 1 1	$-C(=NH)CH_3$	$-CH_2-$
4	H	H	(2)	0 1 1 0	H	$-(CH_2)_2-$
5	H	CH_3	(2)	0 1 1 0	$-C(=NH)CH_3$	$-(CH_2)_2-$
6	H	H	(2)	0 1 1 0	H	$-CH_2-$
7	H	CH_3	(2)	0 1 1 0	H	$-CH_2-$
8	H	H	(2)	0 1 1 0	CH_3	$-CH_2-$
9	H	CH_3	(2)	0 1 1 0	CH_3	$-CH_2-$
10	H	CH_3	(2)	0 1 1 0	$-C(=NH)H$	$-CH_2-$
11	H	CH_3	(2)	0 1 1 0	$-C(=NH)NH_2$	$-CH_2-$
12	H	H	(2)	1 1 1 1	H	s
13	H	CH_3	(2)	1 1 1 1	CH_2CH_2OH	s
14	H	H	(2)	1 1 1 1	$-C(=NH)CH_3$	s
15	H	CH_3	(2)	1 1 1 1	$-C(=NH)CH_3$	s
16	H	H	(2)	1 1 1 1	CH_3	s
17	H	CH_3	(2)	1 1 1 1	CH_3	s
18	H	CH_3	(2)	1 1 1 1	H	d
19	H	CH_3	(2)	1 1 1 1	CH_3	d
20	H	CH_3	(2)	1 1 1 1	$-C(=NH)H$	d
21	H	H	(2)	1 2 1 0	H	s
22	H	CH_3	(2)	1 2 1 0	$-C(=NH)CH_3$	s
23	H	CH_3	(2)	1 3 1 0	CH_3	s
24	H	H	(2)	0 1 0 1	H	-
25	H	CH_3	(2)	0 1 0 1	H	s
26	H	H	(2)	1 0 1 0	H	s
27	H	H	(2)	1 0 1 0	$-C(=NH)CH_3$	s

(0057) (0058)

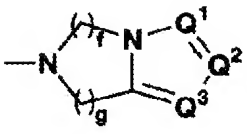
Table 2



No.	R^1	R^2	Form	a b c d	R^9	R^{10}	-B-	X^-
28	H	H	(3)	1 1 1 1	CH_3	CH_3	$-CH_2-$	Cl^-
29	H	H	(3)	1 1 1 1	CH_3	CH_2CH_2OH	$-CH_2-$	Cl^-
30	H	H	(3)	0 1 1 0	CH_3	CH_2CONH_2	$-(CH_2)_2-$	Cl^-
31	H	H	(3)	0 1 1 0	CH_3	CH_2CN	$-CH_2-$	I^-
32	H	H	(3)	0 1 1 0	CH_3	CH_3	s	Cl^-
33	H	H	(3)	1 1 1 1	CH_3	CH_2CONH_2	s	Cl^-
34	H	H	(3)	1 1 1 1	CH_3	CH_3	d	$CF_3SO_3^-$
35	H	H	(3)	1 2 1 0	CH_3	CH_2CH_2OH	s	Cl^-
36	H	H	(3)	1 3 1 0	CH_3	CH_3	d	Cl^-
37	H	CH_3	(3)	0 1 0 1	CH_3	CH_2CH_2OH	s	Cl^-

(0059) (0060)

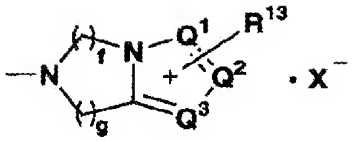
Table 3



No.	R^1	R^2	Form	f	g	Q^1	Q^2	Q^3
38	H	H	(4)	2	1	N	N	CH
39	H	CH_3	(4)	2	1	N	N	CH
40	H	H	(4)	2	1	N	CH	CH
41	H	CH_3	(4)	2	1	N	CH	CH
42	H	H	(4)	2	1	CCH_3	N	CH
43	H	H	(4)	2	1	CH	N	CH
44	H	H	(4)	2	1	CH	N	CCH_3
45	H	CH_3	(4)	2	1	CCH_2OH	N	CH
46	H	H	(4)	2	1	CCH_2OH	N	CH
47	H	H	(4)	2	1	CNH_2	N	CH
48	H	CH_3	(4)	2	1	CNH_2	N	CH
49	H	H	(4)	2	1	$CNH(CH_2)_2OH$	N	CH
50	H	H	(4)	2	1	CCH_2CONH_2	N	N
51	H	H	(4)	2	1	N	N	N
52	H	CH_3	(4)	2	1	N	N	N

(0061) (0062)

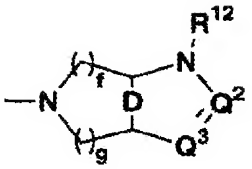
Table 4



No.	R^1	R^2	Form	f	g	Q^1	Q^2	Q^3	R^{13}		X^-
53	H	H	(5)	2	1	N	N	CH	CH_3	(Q^2)	Cl^-
54	H	H	(5)	2	1	N	N	CH	CH_2CH_2OH	(Q^2)	Cl^-
55	H	H	(5)	2	1	N	N	CH	CH_2CONH_2	(Q^2)	Cl^-
56	H	H	(5)	2	1	CH	CH	N	CH_3	(Q^3)	Cl^-
57	H	CH_3	(5)	2	1	CH	CH	N	CH_3	(Q^3)	Cl^-
58	H	H	(5)	2	1	CH	N	N	CH_3	(Q^3)	Cl^-
59	H	CH_3	(5)	2	1	CH	N	N	CH_3	(Q^3)	Cl^-
60	H	H	(5)	2	1	N	CH	CH	CH_3	(Q^1)	Cl^-
61	H	H	(5)	2	1	N	CH	CH	CH_2CH_2OH	(Q^1)	Cl^-
62	H	H	(5)	2	1	N	CH	CH	CH_2CN	(Q^1)	Br^-
63	H	H	(5)	2	1	CH	N	CH	CH_3	(Q^2)	Cl^-
64	H	H	(5)	2	1	CCH_2OH	N	CH	CH_3	(Q^2)	Cl^-
65	H	H	(5)	2	1	CH	N	CH	CH_2CH_2OH	(Q^2)	Cl^-
66	H	H	(5)	2	1	CCH_3	N	CH	CH_2CH_2OH	(Q^2)	Cl^-
67	H	H	(5)	2	1	CCH_3	N	CH	CH_3	(Q^2)	Cl^-
68	H	H	(5)	2	1	CH	N	CCH_3	CH_3	(Q^2)	Cl^-

(0063) (0064)

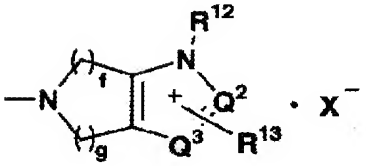
Table 5



No.	R^1	R^2	Form	f	g	Q^2	Q^3	R^{12}	-D-
69	H	H	(6)	1	1	CH	N	H	s
70	H	CH_3	(6)	1	1	CCH_3	N	H	s
71	H	H	(6)	1	1	CH	N	H	d
72	H	CH_3	(6)	1	1	CNH_2	N	H	d
73	H	H	(6)	1	1	CH	N	CH_3	d
74	H	H	(6)	2	1	CH	N	H	d
75	H	CH_3	(6)	2	1	CH	N	CH_3	d
76	H	CH_3	(6)	2	1	N	N	H	d
77	H	CH_3	(6)	1	1	CH	N	CH_2CH_2OH	d

(0065) (0066)

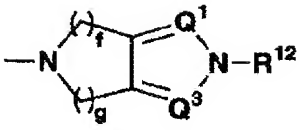
Table 6



No.	R^1	R^2	Form	f	g	Q^2	Q^3	R^{12}	R^{13}	X^-
78	H	H	(7)	2	1	CH	N	CH_3	CH_3 (Q^3)	Cl^-
79	H	H	(7)	2	1	N	N	CH_3	CH_3 (Q^3)	Cl^-
80	H	H	(7)	2	1	CH	N	CH_3	CH_2CH_2OH (Q^3)	Cl^-

(0067) (0068)

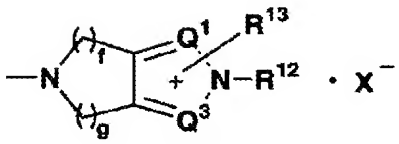
Table 7



No.	R^1	R^2	Form	f	g	Q^1	Q^3	R^{12}
81	H	H	(8)	1	1	CH	CH	H
82	H	CH_3	(8)	1	2	CH	CH	H
83	H	H	(8)	1	1	N	CH	CH_3

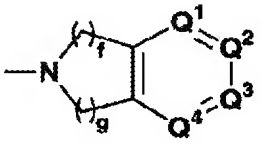
(0069) (0070)

Table 8



No.	R^1	R^2	Form	f	g	Q^1	Q^3	R^{12}	R^{13}	X^-
84	H	H	(9)	1	1	N	CH	CH_3	$CH_3(Q^1)$	Cl^-
85	H	H	(9)	0	2	CH	N	CH_3	$CH_3(Q^1)$	Cl^-
86	H	CH_3	(9)	1	2	CH	N	CH_2H_2OH	$CH_3(Q^1)$	Cl^-

(0071)



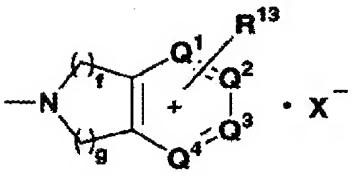
(0072)

Table 9

No.	R^1	R^2	Form	f	g	Q^1	Q^2	Q^3	Q^4
87	H	H	(10)	1	1	N	CH	CH	CH
88	H	H	(10)	1	1	CH	N	CH	CH
89	H	CH_3	(10)	1	1	N	CH	N	CH
90	H	CH_3	(10)	1	1	N	CH	CH	N
91	H	H	(10)	0	2	CH	N	CH	N
92	H	CH_3	(10)	1	2	N	CH	N	CH

(0073) (0074)

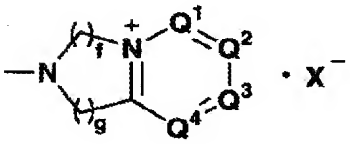
Table 10



No.	R^1	R^2	Form	f	g	Q^1	Q^2	Q^3	Q^4	R^{13}	X^-
93	H	H	(11)	1	1	N	CH	N	CH	$CH_3(Q^3)$	Cl^-
94	H	CH_3	(11)	1	1	N	CH	N	CH	$CH_2CN(Q^3)$	Cl^-
95	H	H	(11)	0	2	CH	N	CH	N	$CH_3(Q^3)$	Cl^-
96	H	CH_3	(11)	0	2	N	CH	CH	N	$CH_3(Q^3)$	Cl^-

(0075) (0076)

Table 11



No.	R^1	R^2	Form	f	g	Q^1	Q^2	Q^3	Q^4	X^-
97	H	H	(12)	2	1	CH	CH	CH	CH	Cl^-
98	H	CH_3	(12)	2	1	CH	CH	CH	CH	Cl^-
99	H	H	(12)	2	1	CH	CCH_2OH	CH	CH	Br^-
100	H	H	(12)	2	1	CH	N	CH	CH	Cl^-

Among the aforesaid ideal compounds, 6, 8, 14, 17, 29, 32, 42, 47, 53, 60, 64, 71 and 100 are proposed as more preferable compounds.

(0077)

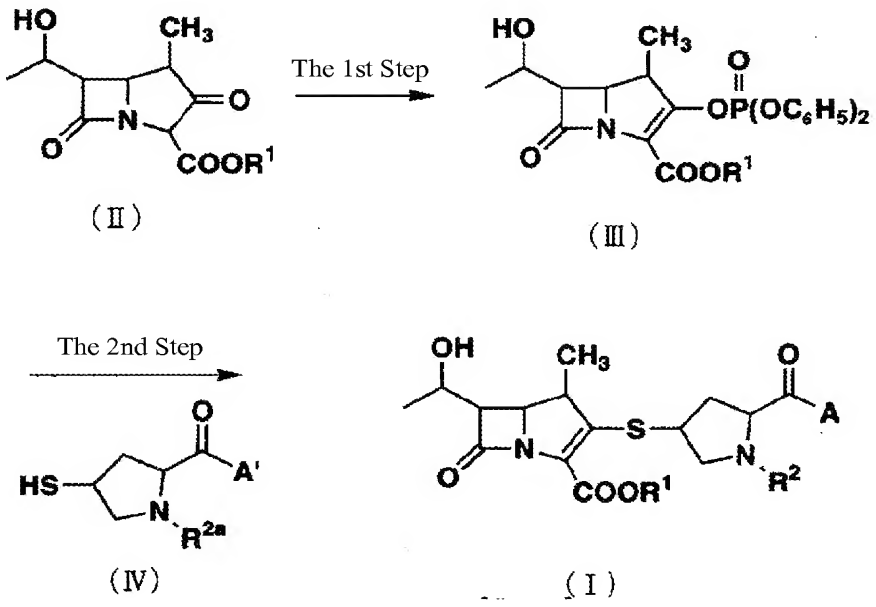
In the compounds of this invention (I), various kinds of isomers on the basis of asymmetric carbon are present. Among such isomers, preferable example is a compound wherein coordination of the carbon corresponding to the 1 position of carbapenem skeleton (the carbon with the methyl group) represented by thienamycin is in the R coordination, and the coordination of carbons corresponding to the 5 and 6-positions are (5S, 6S) coordination, which is the same coordination as thienamycin and the coordination of the carbon of the 6-position substituent α position of the ethyl group having the hydroxy group is the R coordination.

(0078)

The compounds of this invention (1) can be produced according to the following step procedure A or B.

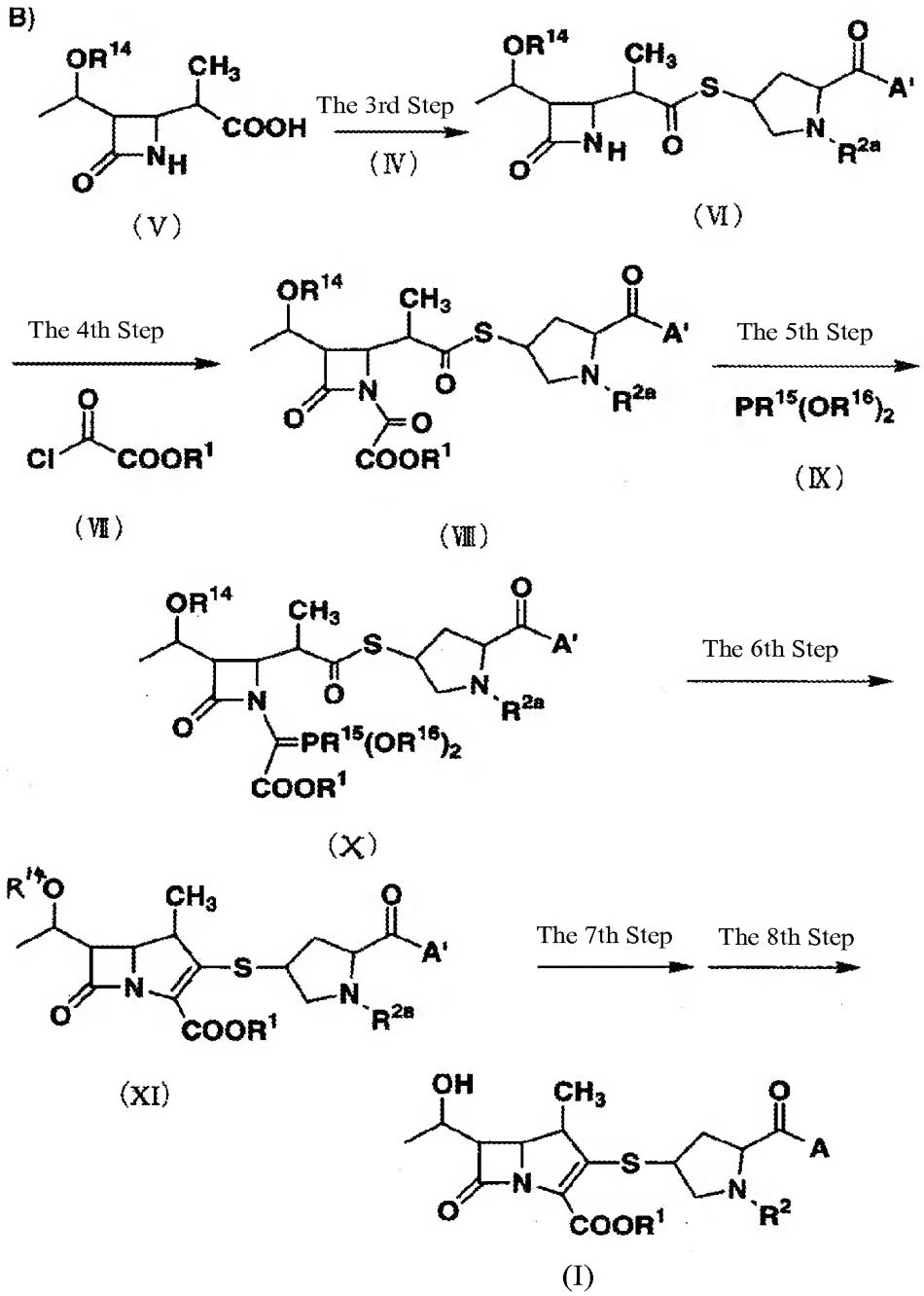
(0079)

A)



(Ⅱ) (Ⅲ) (Ⅳ) (Ⅰ)

(0080)



(0081)

In the aforesaid step progress A and B, R^1, R^2 and A have the same definitions as described above, and A' denotes group corresponding to formulae (3), (5), (7), (9), (11) and (12) of A in the said formula (1) which forms quaternary ammonium salt by alkylation, and R^{14} denotes protecting group of hydroxy group (preferably trialkylsilyl group such as trimethylsilyl group, alkenyl carbonyl group such as allyl

oxycarbonyl group or alkoxycarbonyl group such as methoxycarbonyl group, or aralkyl oxycarbonyl group such as p-nitrobenzyl oxycarbonyl group), R^{15} deonotes lower alkyl group (particularly methyl group), lower alkoxy group (particularly methoxy group) or aryloxy group (particularly phenyloxy group) and R^{16} denotes lower alkyl group (particularly methyl group) or aryl group (particularly phenyl group) .

(0082)

A) Synthesis method via 2-phosphoester

Diphenyl phosphoryl chloride is caused to react with well known ketocarboxylic acid derivative (II) (literature: D.H.Shih et al., "Heterocycles 21, 29 (1984)") in the presence of base in a suitable solvent to form inert compound (III) and thereafter, by carrying out substitutional reaction of thiol compound (IV) in a suitable solvent, compounds of this invention (I) can be obtained.

(0083)

Each step will now be described in greater detail.

1st Step

This step is a step to obtain compound (III) by reacting diphenyl phosphoryl chloride with compound (II) in the presence of base in inert solvent.

(0084)

This step can be carried out according to well known method, for example the method of D.H.Shih et al., "Heterocycles 21, 29 (1984)" or process in accordance with this.

(0085)

As far as the solvent used is concerned, there is no restriction in particular so long as the said solvent does not exert a harmful effect on the reaction. However, for example, preferably halogenated hydrocarbons such as methylene chloride, chloroform or the like, ethers such as diethyl ether, tetrahydrofuran or the like, nitriles such as acetonitrile or the like, amides such as dimethylformamide or the like, sulphoxides such as dimethylsulfoxide or the like, or mixed solvent of these.

(0086)

As the base used, an organic base such as triethylamine, diisopropyl ethylamine, N-methylmorpholine, 1,8-diazabicyclo[5.4.0]-7-undecene or the like, metal alcoholates such as sodium methoxide, potassium t-butoxide or the like may be proposed, and diisopropyl ethylamine is in particular preferred.

(0087)

The reaction temperature is usually -50°C to room temperature, particularly preferably -20°C to 0°C, and the reaction time differs depending on the starting material, reaction temperature and the like, but usually 15 mins-5 hours, in particular 30 mins-2 hours is preferred.

(0088)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, the reaction mixture is suitably neutralized or when insolubles are present, these are eliminated by filtration, and thereafter an immiscible organic solvent such as water and ethyl acetate are added, washed with water, and the organic layer including the target compound is separated, dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. Usually obtained target compound is used in following step without carrying out isolation procedure, but if necessary, it can be further purified by normal procedures, for example recrystallization, reprecipitation or chromatography.

(0089)

2nd Step

This step is a step to obtain the compound of this invention (I) by reacting thiol compound (IV) with compound (III) in inert solvent.

(0090)

As solvent used, similar solvent as in 1st Step may be proposed, but when the reaction is carried out without isolation of compound (III), it is preferable to use completely identical solvent to that used in 1st Step.

(0091)

The reaction temperature is usually -50°C to room temperature, particularly preferably -20°C to 0°C, and the reaction time differs depending on the starting material, reaction temperature and the like, but usually 30 mins-15 hours, particularly 1-6 hour is preferred.

(0092)

A base is preferably used in order to proceed this step smoothly.

(0093)

As the base used, organic base such as triethylamine, diisopropyl ethylamine, 1,8-diazabicyclo[5.4.0]-7-undecene or the like is preferred.

(0094)

Moreover, in this step, thiol compound (IV) is preferably used in an amount of 1-1.5 equivalents of compound (III), and moreover it is preferred that thiol compound (IV) and base are usually used in equivalent amounts.

(0095)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, the reaction mixture is suitably neutralized or when insolubles are present, these are eliminated by filtration, and thereafter an immiscible organic solvent such as water and ethyl acetate is added, and the mixture washed with water, and the organic layer including the target compound is separated, dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. The obtained target compound can be further purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0096)

B) Synthesis method using cyclization reaction by Intermolecular Wittig Reaction

Mercaptan derivative (IV) is caused to react with well known carboxylic acid derivative (V) (literature: D.H.Shih et al., "Heterocycles 21, 29 (1984)") in the presence of condensing agent to produce compound (VI), and thereafter, alkoxy oxalyl chloride (VII) is reacted, and compound (VIII) is obtained. Moreover, phosphorus compound (IX) is reacted with compound (VIII) to derive phosphonium ylide (X), and by further heating (X), it is possible to obtain compound (XI) having carbapenem skeleton. By eliminating protecting group R^{14} of hydroxy group in (XI), compound wherein A is A' among the compounds of this invention (I) can be obtained. To obtain the compound wherein A has quaternary ammonium salt structure among the compounds of this invention (I), quaternisation of the amino group contained in A' of compound (I) may be carried out alkylation by reacting with suitable alkylating agent.

(0097)

Each step will now be explained in greater detail.

(0098)

3rd Step

This step is a step to obtain compound (VI) by reacting mercaptan derivative (IV) with compound (V) in the presence of condensing agent in inert solvent.

(0099)

As solvent used, there is no restriction in particular as long as it does not hinder the reaction, but preferably aromatic hydrocarbon such as benzene, toluene and the like, halogenated hydrocarbons such as methylene chloride, chloroform and the like, esters such as ethyl acetate and the like, ethers such as tetrahydrofuran, diethyl ether and the like are used.

(0100)

As condensing agent used, preferably N,N'-dicyclohexylcarbodiimide, N,N'-carbonyldiimidazole or diphenyl phosphoryl azide-triethylamine are used.

(0101)

The reaction temperature is usually -20° to 50°C, and the reaction time differs depending on the starting material, reaction temperature and the like, but is usually 30 mins-5 hours.

(0102)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, the reaction mixture is suitably neutralized by decomposing excess reagent by adding water, or when insolubles are present, these are eliminated by filtration, and thereafter an organic solvent immiscible with water such as ethyl acetate is added, and the mixture washed with water, and the organic layer including the target compound is separated, dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. The obtained target compound can be further purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0103)

4th Step

This step is a step to obtain compound (VIII) by reacting alkoxy oxalyl chloride (VII) with compound (VI) in the presence of base in inert solvent.

(0104)

As solvent used, preferably halogenated hydrocarbons such as methylene chloride, chloroform and the like, ethers such as tetrahydrofuran, dioxane and the like, aromatic hydrocarbon such as benzene, toluene and the like, nitriles such as acetonitrile and the like are used.

(0105)

As base used, preferably organic base such as triethylamine, diisopropylamine, 1,8-diazabicyclo[5.4.0]-7-undecene or the like is used.

(0106)

The reaction temperature is usually -50°C to room temperature, particularly preferably -20°C to 0°C. The reaction time differs depending on the starting material, reaction temperature and the like, but is usually 30 mins-5 hours.

(0107)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, the reaction mixture is added to water and when insolubles are present, these are eliminated by filtration, and thereafter an organic solvent which is immiscible with water such as ethyl acetate is added, and after washing with water, the organic layer including the target compound is separated, dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. The obtained target compound can be further purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0108)

5th Step

This is a step to obtain compound (X) by reacting phosphorus compound (IX) with compound (VIII) in inert solvent or without solvent.

(0109)

In this step, phosphorus compound (IX) is usually used in an amount of 2-6 mole equivalents with respect to compound (VIII).

(0110)

As the solvent which is used when solvent is used, as long as it is an aprotic solvent, there is no limit in particular. However, it preferably aliphatic hydrocarbon such as hexane and the like, aromatic

hydrocarbon such as benzene, toluene, xylene and the like, halogenated hydrocarbons such as chloroform, methylene chloride, 1,2-chloroethane and the like, esters such as ethyl acetate and the like, ethers such as tetrahydrofuran, dioxane and the like, nitriles such as acetonitrile and the like or amides such as dimethylformamide, dimethylacetamide and the like.

(0111)

The reaction temperature at usually 30-100°C and the reaction time differs depending on the starting materials and the reaction temperature, but usually is 2-20 hours.

(0112)

As phosphorus compound (IX) used, lower alkyl phosphite such as trimethyl phosphite, triethyl phosphite, triisopropyl phosphite or the like, phosphonous acid dialkyl ester such as methyl phosphonous acid dimethyl, methyl phosphonous acid diethyl, methyl phosphonous acid dipropyl, ethyl phosphonous acid dimethyl, ethyl phosphonous acid diethyl, ethyl phosphonous acid diisopropyl or the like may be proposed.

(0113)

After completion of the reaction, by eliminating under reduced pressure by distillation acid adduct (organophosphate or phosphonic ester) which is formed from the solvent, unreacted (IX) and (IX), compound (X) is obtained. The crude product (X) obtained in this way can be used in the following step without being purified or any further treatment, but in accordance with requirements, can be purified by using column chromatography or the like.

(0114)

6th Step

This step is a step obtaining cyclization compound (XI) by heating compound (X) in inert solvent.

(0115)

As solvent used, preferably aromatic hydrocarbon such as benzene, toluene, xylene, mesitylene, chlorobenzene and the like is used.

(0116)

The reaction temperature is usually 50-170°C and preferably 100-160°C.

(0117)

The reaction time differs depending on the starting materials and the reaction temperature, but usually it is 2-30 hours.

(0118)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, the solvent is eliminated by distillation from the reaction mixture, and the obtained residue can be purified by carrying out normal procedures, for example recrystallisation, reprecipitation, chromatography or the like.

(0119)

7th Step

This step is a step to obtain the compound of this invention (I) by eliminating the protecting group of compound (IX) in inert solvent.

(0120)

The elimination of the protecting groups differs depending on the kind of protecting group, but a conventionally used process can be applied.

(0121)

For example in the case that protecting group is a trimethylsilyl group, it may be eliminated by treating with potassium fluoride in the presence of acetic acid in methanol or with pyridinium-p-toluenesulfonic acid in water-tetrahydrofuran. Moreover, when protecting group is allyl oxycarbonyl group, elimination can be carried out by reacting tetrakis triphenylphosphine palladium (O), triphenylphosphine and 2-ethyl hexanoic acid in aprotic solvent such as tetrahydrofuran or the like. Moreover, when protecting group is p-nitrobenzyl oxycarbonyl group, it can be carried out by catalytic reduction method using metal catalyst such as palladium-carbon or the like.

(0122)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, after dissolving insolubles by suitably adding water to the reaction mixture, or eliminating by filtration when metal catalyst and the like is present, an organic solvent which is immiscible with water such as ethyl acetate is added, and after the liquid separation, the aqueous layer including the target compound is separated, concentrated under reduced pressure, and thereafter, the target compound is obtained by refining the liquid concentrate by reverse phase chromatography.

(0123)

8th Step

This step is a step selectively carried out in order to obtain compound having quaternary ammonium salt structure among the compounds of this invention (I) in inert solvent.

(0124)

As solvent used, preferably nitriles such as acetonitrile, ethers such as tetrahydrofuran.

(0125)

Alkylating agent used differs depending on desired compound, but alkyl iodide species such as alkyl methyl iodide, an alcohol iodide such as 2-iodo ethanol, acylamido iodide species such as α-iodoacetamide, sulphonic acid ester such as methyl trifluoromethanesulfonate, methyl fluoro sulphonate (magic methyl) and the like are used.

(0126)

The reaction temperature is usually 0-100°C and preferably 0-50°C. The reaction time differs depending on the starting materials and the reaction temperature, but is usually 30 mins-5 hours. After completion of the reaction, the target compound of this step is usually subjected to elimination reaction of protecting groups immediately without being isolated and purified, and the target compound is obtained by refining by reverse phase chromatography in the same aforesaid way. Further the obtained target compound can be purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0127)

The compound of this invention (I) can be formed into a pharmacologically permitted salt, and as salts thereof, metal salt such as sodium, potassium, aluminum, magnesium and the like, amine salt such as triethylamine, procaine, benzylamine and the like may be proposed, but sodium salt and potassium salt are in particular preferred.

(0128)

Moreover, because basic group is present in carbapenem derivative of this invention, it can be made into pharmacologically permitted acid addition salt such as for example salt of mineral acid such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and the like or salt of organic acid such as acetic acid, citric acid, succinic acid, methanesulfonic acid or the like, and as the particularly

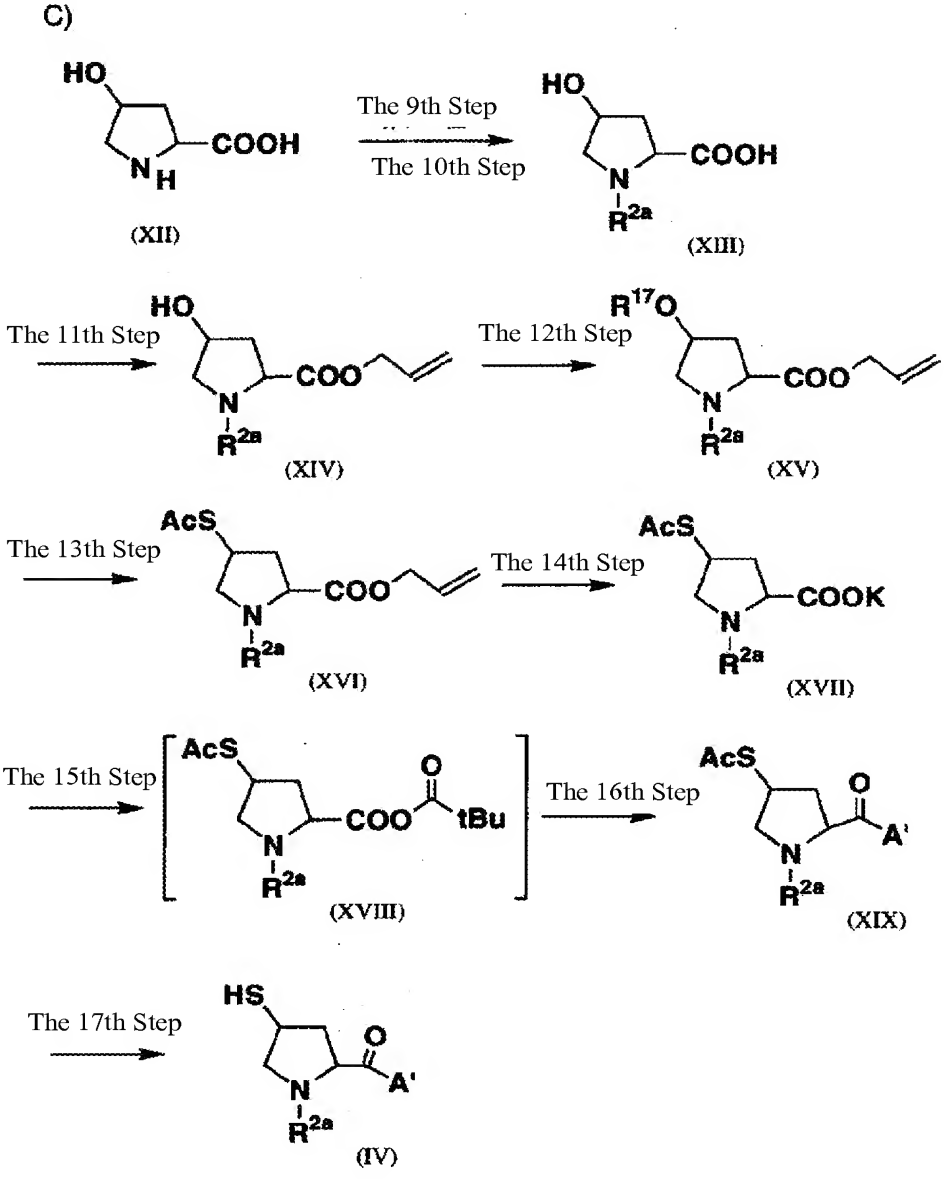
preferable salt, hydrochloride and sulfate may be proposed.

(0129)

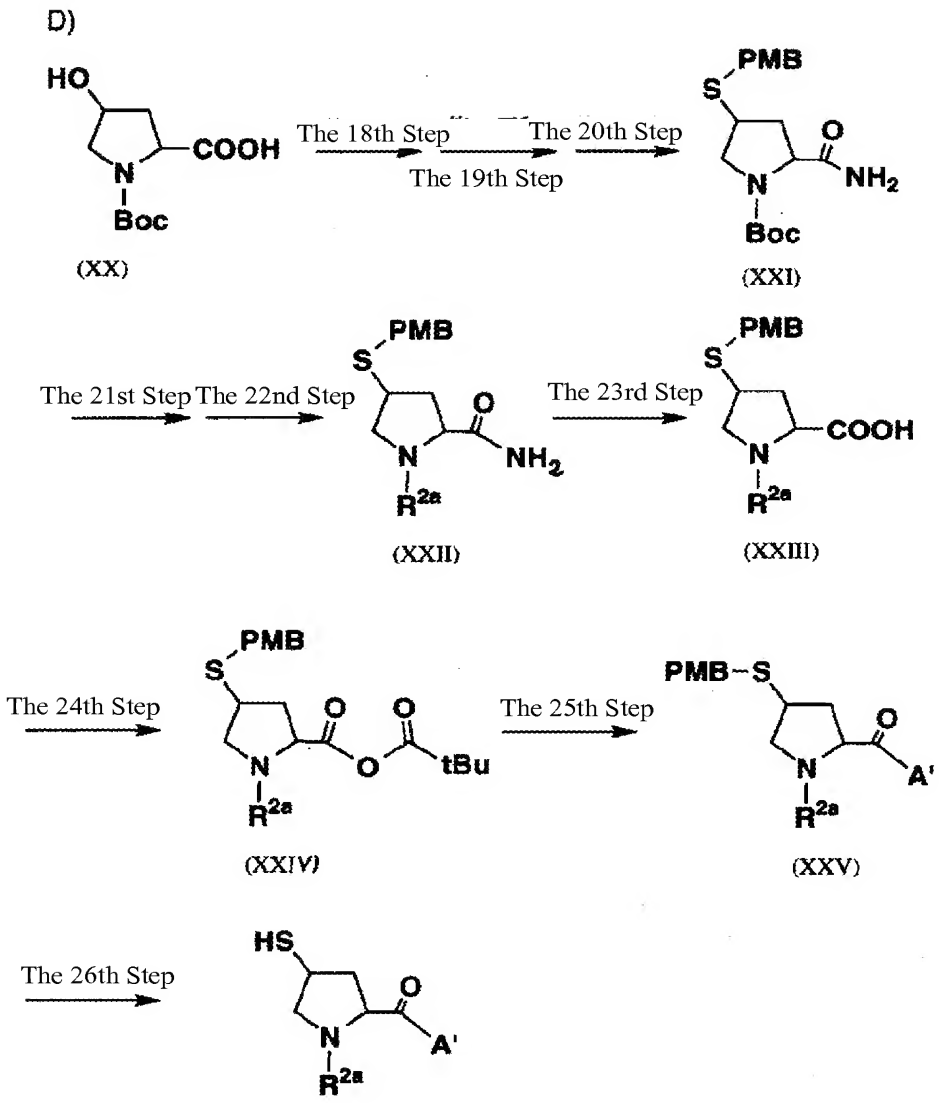
In order to produce the compound of this invention, compound (IV) which is used as a starting material can be produced using the following process C or D.

(0130)

C)



(0131)



(0132)

Process C) The case when R^{2a} is protecting group or protected imidoyl group:

9th Step

This step is a step to obtain compound (XIII) (wherein, R^{2a} is $-C(=NR^3)R^4$) by reacting R^4-C(=NH)-NHR^3 (R^3 and R^4 have the same aforesaid meanings) with compound (XII) in the presence of hydrochloric acid / dioxane solution (preferably 4N) in acetonitrile.

(0133)

The reaction temperature is usually 0-70°C, and the reaction time is usually 1-5 hours. After completion

of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, the reaction mixture is suitably neutralized or when insolubles are present, these are eliminated by filtration, and thereafter an immiscible organic solvent such as water and ethyl acetate is added, the mixture is washed with water, and the organic layer including the target compound is separated, dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. The obtained target compound can be further purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0134)

10th Step

This step is a step to obtain compound (XIII) by reacting protection reagent (preferably p-nitrobenzyl oxycarbonyl chloride) of amino group with compound (XII) in the presence of base (preferably hydroxide such as sodium hydroxide, potassium hydroxide) in a mixed solvent of water and ether such as tetrahydrofuran; and moreover it is a step to carry out with the 9th Step alternatively.

(0135)

Usually the reaction temperature is -20 to 50°C, and the reaction time is usually from 30 minutes to 5 hours.

(0136)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, the reaction mixture is suitably neutralized or when insolubles are present, these are eliminated by filtration, and thereafter an immiscible organic solvent such as water and ethyl acetate is added, the mixture is washed with water, and the organic layer including the target compound is separated, dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. The obtained target compound can be further purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0137)

11th Step

This is a step to obtain compound (XIV) by reacting allyl bromide on compound (XIII) in the presence of base (preferably tertiary organic amine such as triethylamine) in a halogenated hydrocarbon such as methylene chloride.

(0138)

Usually the reaction temperature is -10 to 50°C, and the reaction time is usually 1-12 hours.

(0139)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, the reaction mixture is suitably neutralized or when insolubles are present, these are eliminated by filtration, and thereafter an immiscible organic solvent such as water and ethyl acetate is added, the mixture is washed with water, and the organic layer including the target compound is separated, dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. The obtained target compound can be further purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0140)

12th Step

This is a step to obtain compound (XV) by reacting a reagent which forms sulphonic acid ester (preferably sulfonyl halides such as methanesulfonyl chloride, p-toluenesulphonyl chloride) with compound (XIV) in the presence of base (preferably tertiary organic amine such as triethylamine and pyridine) in a halogenated hydrocarbon such as methylene chloride.

(0141)

Usually the reaction temperature is -30 to 50°C, and usually the reaction time is 0.5-12 hours.

(0142)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, to the reaction mixture is added an organic solvent immiscible with water such as ethyl acetate, and, after washing with water, the organic layer including the target compound is separated and dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. Further the obtained target compound can be purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0143)

13th Step

This is a step to obtain compound (XVI) by reacting potassium thioacetate ($CH_3C(=O)SK$) or sodium thioacetate ($CH_3C(=O)SNa$) with compound (XV) in an amide such as dimethylformamide or dimethylacetamide.

(0144)

The reaction temperature is usually 20-100°C, and the reaction time is usually 1-7 hours.

(0145)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, to the reaction mixture is added an organic solvent immiscible with water such as ethyl acetate, and, after washing with water, the organic layer including the target compound is separated and dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. Further the obtained target compound can be purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0146)

14th Step

This step is a step to obtain compound (XVII) by reacting deprotection agent of allyl group (preferably catalytic quantity of $Pd(PPh)_4$ and 2-ethyl hexanoic acid potassium salt are used) with compound (XVI) in esters such as ethyl acetate.

(0147)

The reaction temperature is usually 0-30°C, and the reaction time is usually 1-5 hours.

(0148)

After completion of the reaction, because target compound of this step is usually precipitated as solid body, it is recovered by filtration and is collected.

(0149)

The obtained target compound can be further purified by normal procedures, for example recrystallization or reprecipitation in accordance with requirements.

(0150)

15th Step

This step is a step to obtain compound (XVIII) by reacting pivaloyl chloride on compound (XVII) in a halogenated hydrocarbon such as methylene chloride.

(0151)

Usually the reaction temperature is -20 to 30°C, and usually the reaction time is 0.5-2 hours.

(0152)

After completion of the reaction, because the compound obtained in this step is usually unstable, it is used in the next step immediately without being isolated.

(0153)

16th Step

This step is a step to obtain compound (XIX) by reacting heterocyclic amine corresponding to requirements in the presence of base (preferably tertiary amine such as diisopropyl ethylamine is used) in a halogenated hydrocarbon such as methylene chloride used in the step to obtain compound (XVIII).

(0154)

Usually the reaction temperature is -20 to 30°C, and usually the reaction time is 0.5-2 hours.

(0155)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, the reaction mixture is suitably neutralized, and organic solvent immiscible with water such as ethyl acetate is added, the mixture is washed with water, and the organic layer including the target compound is separated, dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. The obtained target compound can be further purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0156)

17th Step

This step is a step to obtain compound (IV) by reacting in an alcohol such as methanol, ethanol or the like the alkali metal alkoxide (preferably methanol and sodium methoxide) of corresponding alcohol with compound (XIX).

(0157)

Usually the reaction temperature is -20 to 30°C, and usually the reaction time is 0.5-1 hours.

(0158)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, the reaction mixture is suitably neutralized, and the organic solvent immiscible with water such as ethyl acetate is added, and after washing with water, the organic layer including the target compound is separated and dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. Further the obtained target compound can be purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0159)

Process D) The case when R^{2a} is alkyl group, alkenyl group

18th Step

This step is a step to amidate carboxylic acid by treating compound (XX) with ammonia water after reacting with chloroformic acid ethyl ester in an ether such as tetrahydrofuran.

(0160)

Usually the reaction temperature is -20-30°C, and the reaction time is usually 1-3 hours.

(0161)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, the reaction mixture is suitably neutralized, and an organic solvent which is immiscible with water such as ethyl acetate is added, and, after washing with water, the organic layer including the target compound is separated and is dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. Further the obtained target compound can be purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0162)

19th Step

This step is a step to methanesulphonyloxylate the hydroxy group by reacting methanesulfonyl chloride on the amidated compound obtained in the 18th Step in the presence of organic amine species such as triethylamine in an ether such as tetrahydrofuran.

(0163)

Usually the reaction temperature is -20-30°C, and usually the reaction time is 0.5-2 hours.

(0164)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, the reaction mixture is suitably neutralized, and an organic solvent which is immiscible with water such as ethyl acetate is added, and, after washing with water, the organic layer including the target compound is separated and is dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. Further the obtained target compound can be purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0165)

20th Step

This step is a step to obtain compound (XXI) by reacting sodium 4-methoxybenzyl mercaptide with methanesulphonyloxylated compound obtained in the 19th Step in dimethylformamide.

(0166)

The reaction temperature is usually 50-100°C, and the reaction time is usually 1-5 hours.

(0167)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, to the reaction mixture is added an organic solvent immiscible with water such as ethyl acetate, and, after washing with water, the organic layer including the target compound is separated and is dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. Further the obtained target compound can be purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0168)

21st Step

This step is a step to eliminate t-butoxycarbonyl group which is a protecting group of amino group by reacting hydrochloric acid (preferably 4N) in ethyl acetate with compound (XXI).

(0169)

The reaction temperature is usually 0-50°C, and usually the reaction time is 0.5-3 hours.

(0170)

After completion of the reaction, the target compound of this step is collected from the reaction mixture as hydrochloride crystals.

(0171)

Further the obtained target compound can be purified by normal procedures, for example recrystallization or reprecipitation in accordance with requirements.

(0172)

22nd Step

This step is a step to obtain compound (XXII) by reacting dimethylsulfuric acid or alkyl halide with the compound obtained in the 21st Step in the presence of base in an ether such as tetrahydrofuran.

(0173)

The reaction temperature is usually 0-50°C, and the reaction time is usually 1-5 hours.

(0174)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, the reaction mixture is suitably neutralized, and an organic solvent which is immiscible with water such as ethyl acetate is added, and, after washing with water, the organic layer including the target compound is separated and is dried with anhydrous magnesium sulphate and the like, and thereafter, the target compound is obtained by eliminating the solvent by distillation. Further the obtained target compound can be purified by normal procedures, for example recrystallization, reprecipitation or chromatography in accordance with requirements.

(0175)

23rd Step

This step is a step to obtain compound (XXIII) by reacting 2N-hydrochloric acid on compound (XXII) in water-containing methanol.

(0176)

The reaction temperature is usually 20-100°C, and the reaction time is usually 1-5 hours.

(0177)

After completion of the reaction, the target compound of this step is collected from the reaction mixture according to normal procedures. For example, hydrochloride precipitated by concentration of the reaction mixture is isolated and recovered by filtration.

(0178)

24th Step

This step is a step obtaining compound (XXIV) by reacting pivaloyl chloride with compound (XXIII) in the presence of triethylamine in a halogenated hydrocarbon such as methylene chloride, and the step is carried out in the same way as in the 15th Step.

(0179)

Usually the reaction temperature is -20-30°C, and usually the reaction time is 0.5-2 hours.

(0180)

After completion of the reaction, because the target compound of this step is generally unstable, it is used in the next step without isolating as reaction liquid itself.

(0181)

25th Step

This step is a step to obtain compound (XXV) by reacting heterocyclic amine corresponding to requirements with the aforesaid methylene chloride reaction liquid containing compound (XXIV) after adding base (preferably tertiary amine such as diisopropyl ethylamine is used), and the step is carried out in the same way as in the 16th Step.

(0182)

26th Step

This step is a step to obtain compound (IV) by reacting trifluoromethanesulfonate with compound (XXV) in the presence of anisole and trifluoro acetate.

(0183)

Usually the reaction temperature is -20 to 50°C, and usually the reaction time is 1-6 hours. After completion of the reaction, the target compound of this step can be obtained as the crude salt by eliminating the reagent by distillation under reduced pressure, and usually it is used as starting material for the next step without being purified.

(0184)

The carbapenem derivatives of this invention are novel compounds, and have excellent physicochemical stability and stability with respect to enzymes such as β-lactase and the like, and in addition, have an antibacterial activity even with respect to bacteria having resistance to penicillin and cephalosporin antibiotics, and are extremely useful as prevention and treatment agents for infections in humans and animals.

(0185)

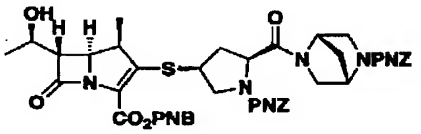
As administrative form of the compound of this invention (I), for example, oral administration by for example tablet, encapsulated formulation, granule, powder, syrup or the like or parenteral administration by for example suppository or injection may be proposed. These preparations may be produced by well-known process using additives such as excipient, binding agent, disintegrating agent, lubricant, stabilizer, flavoring agent and the like. The quantity used thereof differs depending on the symptoms and age and the like, but usually administration to an adult can be made in an amount of 1-200 mg/kg body weight, preferably 1-50 mg/kg body weight per day once a day or several times a day in a divided manner.

(0186)

Example 1

(1R, 5S, 6S)-6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S, 4S) -1-(4- nitrobenzyl oxycarbonyl) -2-(((1S, 4S) -5-(4- nitrobenzyl oxycarbonyl) -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester.

(0187)



(0188)

(2S, 4S) -4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) -2-(((1S, 4S) -5-(4- nitrobenzyl oxycarbonyl) -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine (1.17 g, 1.87 mmol)) was dissolved in a mixed solvent of methanol (7 ml) and tetrahydrofuran (7 ml), and 28 % sodium methoxide - methanol solution (392 μl, 1.86 mmol)) was added under ice cooling. The mixture was stirred under ice cooling for 20 minutes, and next, acetic acid (120 μl, 2.05 mmol)) was added, and the mixture was concentrated. Dichloromethane was added to the residue and, after washing with water, the residue was dried. The solvent was eliminated by distillation, and crude (2S, 4S) -4- mercapto -1-(4- nitrobenzyl oxycarbonyl) -2-(((1S, 4S) -5-(4- nitrobenzyl oxycarbonyl) -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine (1.09 g) was obtained as an oily substance.

Meanwhile, (1R, 5R, 6S), -6-((R)-1- hydroxyethyl)-1- methyl -2- (diphenylphosphoryl oxy) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (1.11 g, 1.86mmol)) was dissolved in acetonitrile (20 ml), and an acetonitrile (10 ml) solution of the above obtained (2S, 4S) -4- mercapto -1-(4- nitrobenzyl oxycarbonyl) -2-(((1S,4S)-5-(4- nitrobenzyl oxycarbonyl) -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine (1.09 g) was added under ice cooling dropwise, and next, diisopropyl ethylamine (700 μl, 4.10 mmol)) was added. The mixture was stirred under ice cooling for three hours, and next, it was concentrated, and dichloromethane was added, and it was washed successively with saturated sodium hydrogen carbonate solution, water and saturated aqueous sodium chloride solution. The solvent was eliminated by distillation under reduced pressure, and the residue was subjected to column chromatography using 80 ml silica gel, and it was eluted with methanol - ethyl acetate (3:20), and pale yellow foamed title compound (1.61 g, 93 %) was thereby obtained.

(0189)

IR spectrum ν_{max} (KBr) cm^{-1}:3400,2969,1773,1709,1656,1607,1522,1346.

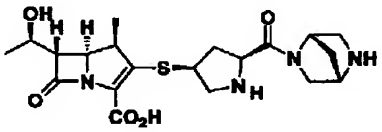
NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.28 (3H, d, J=7Hz), 1.37 (3H, d, J=6Hz), 1.8-2.02 (3H, m),

2.48-2.80 (1H, m), 3.2-4.40 (12H, m), 3.27 (1H, dd, J=7.3Hz), 4.50-4.75 (2H, m), 5.12-5.38 (5H, m), 5.50 (1H, d, J=14Hz), 7.42-7.57 (4H, m), 7.65 (2H, d, J=9Hz), 8.23 (6H, d, J=9Hz).

Example 2.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-2-(((1S,4S)-2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid.

(0190)



(0191)

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-1-(4- nitrobenzyl oxycarbonyl) -2-(((1S,4S)-5-(4- nitrobenzyl oxycarbonyl) -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (1.61 g, 1.74 mmol)) was dissolved in tetrahydrofuran (50 ml) - water (36 ml) mixed solvent, and 10 % palladium - carbon (3.23 g) was added and the mixture was stirred at room temperature under ambient pressure / hydrogen for two hours 30 minutes. The catalyst was separated by filtration, and the filtrate was washed with ether. The aqueous layer was concentrated under reduced pressure and was submitted to reverse phase column chromatography using Cosmosil C-18PREP (made by Nacalai Tesque) 50 g, and the fraction eluted with acetonitrile - water (1:19) was freeze-dried, and the colourless foamed title compound (339 mg, 45 %) was thereby obtained.

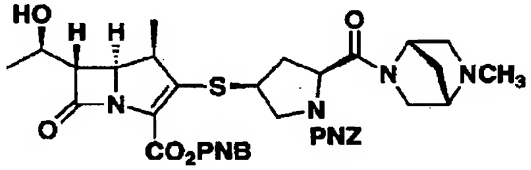
(0192)

IR spectrum ν_{max} (Kbr) cm^{-1}:3409,2968,1759,1657,1591,1459,1384,1287,1259,1181,1146.
NMR spectrum (270 MHz, D2O) δ ppm:1.22 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 1.97-2.22 (3H, m), 3.03-3.18 (2H, m), 3.38 (1H, dt, J=8.2Hz), 3.45-3.53 (4H, m), 3.70 (1H, s), 3.76 (1H, d, J=12Hz), 3.78 (1H, d, J=12Hz), 3.86 (1H, dd, J=11Hz), 4.02-4.13 (1H, m), 4.22-4.30 (2H, m), 4.65-4.68 (1H, m).

Example 3.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-1-(4- nitrobenzyl oxycarbonyl) -2-(((1S,4S)-5- methyl -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester.

(0193)



(0194)

(2S, 4S) -4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) -2-(((1S,4S)-5- methyl -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine (550 mg, 1.19 mmol)) was dissolved in methanol (5 ml), and 28 % sodium methoxide - methanol solution (266 μl, 1.31 mmol)) was added under ice cooling. The mixture was stirred under ice cooling for 20 minutes, and next, acetic acid (75 μl, 1.31 mmol)) was added. Meanwhile, (1R, 3R, 5R, 6S), -6-((R) -1- hydroxyethyl)-1- methyl -2- oxo carba penam -3- carboxylic acid 4- nitrobenzyl ester (517 mg, 1.43 mmol)) was dissolved in acetonitrile (6 ml), and diisopropyl ethylamine (267 μl, 1.57 mmol)) and diphenyl chlorophosphate (321 μl, 1.54 mmol)) were added under ice cooling and the mixture was stirred for one hour.

Furthermore diisopropyl ethylamine (267 μl, 1.57 mmol)) was added, and next, this solution was added to solution of the above obtained (2S, 4S) -4- mercapto -1-(4- nitrobenzyl oxycarbonyl) -2-(((1S,4S)-5- methyl -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine. The mixture was stirred under ice cooling for one hour 30 minutes, and it was concentrated after furthermore having left it to stand in a refrigerator overnight, and dichloromethane was added, and the mixture was washed sequentially with sodium hydrogen carbonate aqueous solution, water and saturated aqueous sodium chloride solution. The solvent was eliminated by distillation under reduced pressure, and the residue was subjected to chromatography of Lobar column, and it was eluted with methanol - dichloromethane (3:20), and pale yellow foamed title compound (460 mg, yield 51 %) was thereby obtained.

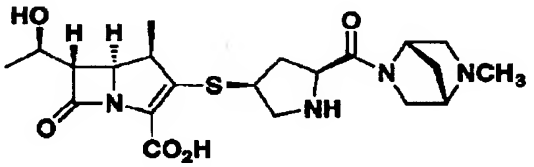
(0195)

IR spectrum ν_{max} (KBr) cm^{-1}:3401,1772,1709,1651,1522,1347,1209,1109.NMR spectrum (270 MHz, $CDCl_3$-CD_3OD) δ ppm:1.28 (3H, d, J=7Hz), 1.33 (3H, d, J=6Hz), 1.74-2.08 (3H, m), 2.40 (3H x 1/3,s), 2.44 (3H x 2/3,s), 2.67-3.10 (3H, m), 3.21-3.90 (8H, m), 4.03-4.60 (4H, m), 5.06 and 5.19 (2H X1/2,ABq, J=13Hz), 5.21 (2H x 1/2,s), 5.26 and 5.49 (2H, ABq, J=14Hz), 7.53 and 8.22 (4H, A2B2,J=9Hz), 7.67 and 8.22 (4H, A2B2,J=9Hz).

Example 4.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-2-(((1S,4S)-5- methyl -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid.

(0196)



(0197)

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-1-(4- nitrobenzyl oxycarbonyl) -2-(((1S,4S)-5- methyl -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl)-4- pyrrolidinyl) thio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (202 mg, 0.264 mmol)) was dissolved in tetrahydrofuran (5ml)- water (5 ml) mixed solvent, and 10 % palladium - carbon (300 mg) was added and the mixture was stirred at room temperature under ambient pressure / hydrogen for two hours 30 minutes. The catalyst was separated by filtration, and washed with ether, and the filtrate was concentrated under reduced pressure. The liquid (about 6 ml) was concentrated and subjected to reverse phase column chromatography CHP-20P (made by Mitsubishi Kasei, 54 ml), and the fraction eluted with acetone - water (1:19) was freeze-dried, and the colourless foamed title compound (46 mg, yield 39 %) was thereby obtained.

(0198)

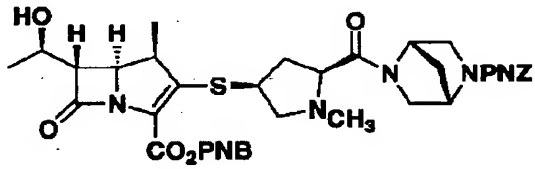
IR spectrum ν_{max} (KBr) cm^{-1}:3416,2968,1755,1657,1594,1459,1384,1288,1149.

NMR spectrum (270 MHz, D2O) δ ppm:1.22 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 1.97-2.07 (1H, m), 2.17-2.47 (2H, m), 3.01 (3H, s), 3.02-3.13 (1H, m), 3.33-3.45 (3H, m), 3.48 (1H, dd, J=6,3Hz), 3.68-3.92 (5H, m), 4.00-4.20 (1H, m), 4.23 (1H, d, J=3Hz), 4.23-4.30 (1H, m), 4.47-4.71 (2H, m).

Example 5.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-1- methyl -2-(((1S,4S)-5-(4- nitrobenzyl oxycarbonyl) -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester.

(0199)



(0200)

Trifluoroacetic acid (10 ml) and trifluoromethanesulfonic acid (0.323 ml, 3.7 mmol)) were added under

ice cooling successively to mixture of (2S, 4S)-4-(4- methoxybenzyl thio) -1- methyl -2-(((1S,4S)-5-(4-nitrobenzyl oxycarbonyl) -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine (996 mg, 1.84 mmol)) and anisole (1.99 ml, 1.84 mmol)). Ice bath was removed and the mixture was stirred for 40 minutes, and next, it was concentrated, and the residue was washed with ether.

Next, the residue was dissolved in ethyl acetate, and it was washed successively with saturated aqueous sodium hydrogen carbonate and water. The solvent was eliminated by distillation under reduced pressure, and the residue was subjected to silica gel (50 ml) column chromatography, and it was eluted with a mixed solvent of methanol - dichloromethane (1:10), and pale yellow foamed (2S, 4S) -4-mercapto -1- methyl -2-(((1S,4S)-5-(4- nitrobenzyl oxycarbonyl) -2 ,5- diazabicyclo (2.2.1) heptane -2-yl) carbonyl) pyrrolidine (744 mg) was obtained.

Meanwhile, (1R, 5R, 6S), -6-((R)-1- hydroxyethyl)-1- methyl -2- (diphenylphosphoryl oxy) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (1.19 g, 2.01mmol)) was dissolved in acetonitrile (20 ml), and acetonitrile (10 ml) solution of the above obtained (2S,4S)-4- mercapto -1- methyl -2-(((1S,4S)-5-(4- nitrobenzyl oxycarbonyl) -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine was added under ice cooling, and next, ethyl diisopropylamine (760 μl, 4.42 mmol)) was added. The mixture was stirred under ice cooling for three hours and at room temperature for four hours, and next, it was concentrated, and ethyl acetate was added, and it was washed sequentially with saturated aqueous sodium hydrogen carbonate, water and saturated aqueous sodium chloride solution. The solvent was eliminated by distillation under reduced pressure, and the residue was subjected to column chromatography using silica gel 120 ml, and it was eluted with ethyl acetate - dichloromethane - methanol (5:5:1), and pale yellow foamed title compound (832 mg, yield 54 %) was thereby obtained.

(0201)

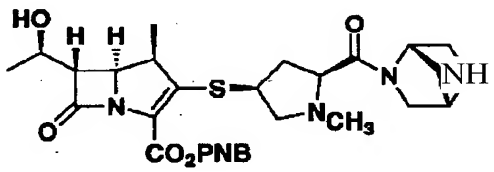
IR spectrum ν_{max} (KBr) cm^{-1}:3402,1771,1708,1640,1522,1441,1346,1208,1179,1137,1106.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.27 (3H, d, J=7Hz), 1.37 (3H, d, J=6Hz), 1.55-2.02 (5H, m), 2.28 (3H x 1/3,s), 2.34 (3H x 2/3,s), 2.47-2.80 (2H, m), 2.93-3.82 (9H, m), 4.18-4.32 (2H, m), 4.53-4.71 (1H, m), 5.12-5.29 (3H, m), 5.50 (1H, d, J=14Hz), 7.52 (2H, d, J=8Hz), 7.66 (2H, d, J=9Hz), 8.21 (2H, d, J=9Hz), 8.22 (2H, d, J=9Hz).

Example 6.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-1- methyl -2-(((1S,4S)-2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid.

(0202)



(0203)

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-1- methyl -2-(((1S,4S)-5-(4- nitrobenzyl oxycarbonyl) -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem - 3- carboxylic acid 4- nitrobenzyl ester (380 mg, 0.497 mmol)) was dissolved in a mixed solvent of tetrahydrofuran (10 ml) - water (10 ml), and 10 % palladium - carbon (570 mg) was added and the mixture was stirred at room temperature under ambient pressure / hydrogen for two hours 30 minutes. The catalyst was separated by filtration, and the filtrate was washed with ether, and next the aqueous layer was concentrated under reduced pressure, and it was subjected to the reverse phase column chromatography using CHP-20P (made by Mitsubishi Kasei, 110 ml), and the fraction eluted with acetone - water (1:19) was recovered, and it was freeze-dried, and the colourless foamed title compound (69 mg, yield 31 %) was thereby obtained.

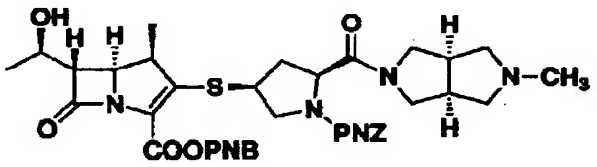
(0204)

IR spectrum ν_{max} (KBr) cm^{-1}:3387,2968,1759,1657,1596,1455,1384,1224,1180,1147.
NMR spectrum (270 MHz, D2O) δ ppm:1.21 (3H, d, J=7Hz), 1.29 (3H, d, J=6Hz), 1.97-2.33 (3H, m), 2.92 (3H x 1/2,s), 2.96 (3H x 1/2,s), 3.17-3.40 (2H, m), 3.43-3.55 (3H, m), 3.63-3.92 (5H, m), 4.14-4.29 (3H, m), 4.39 (1H x 1/2,t, J=9Hz), 4.60 (1H x 1/2,t, J=9Hz), 4.66 (1H, d, J=9Hz).

Example 7.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-2-((7- methyl -3 ,7- diazabicyclo (3.3.0) octane -3- yl] carbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester.

(0205)



(0206)

(1R, 3R, 5R, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2- oxo carba penam -3- carboxylic acid 4- nitrobenzyl ester (1.27 g, 3.50 mmol)) was dissolved in acetonitrile (20 ml) and diisopropyl ethylamine (499 mg, 3.86 mmol)) and diphenyl chlorophosphate (939 mg, 3.50 mmol)) were added under ice cooling and the mixture was stirred at the same temperature for 20 minutes.
Furthermore diisopropyl ethylamine (499 mg, 3.86 mmol)) was added, and next, (2S,4S)-4- mercapto -2-((7- methyl -3 ,7- diazabicyclo (3.3.0) octane -3- yl] carbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine (1.38 g, 3.18 mmol)) was added.

The mixture was stirred for 15 hours under ice-cold, and next, dilute sodium carbonate solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, and the solvent was eliminated by distillation under reduced pressure, and the residue was subjected to chromatography using silica gel 40 g, and it was eluted with methanol : ethyl acetate (12:88-30:70). The oily residue obtained by elimination by distillation of the solvent was dissolved in ethyl acetate 100 ml and dilute sodium carbonate was added with ice cooling and was under ice cooling stirred for five minutes. It was filtered with celite, and the organic layer of the filtrate was separated and was washed with saturated aqueous sodium chloride solution. The solvent was eliminated by distillation under reduced pressure, and it was azeotroped twice with toluene (100 ml), and the title compound (1.79 g, yield 72 %) was thereby obtained.

(0207)

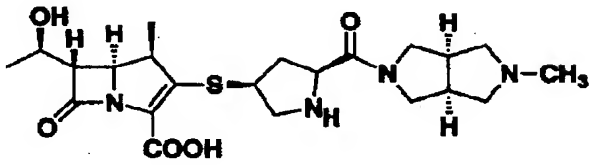
IR spectrum ν_{max} (KBr) cm^{-1}:3380,2689,1755,1641,1460,1386.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.27 (3H x 1/2,d, J=7Hz), 1.28 (3H x 1/2,d, J=7Hz), 1.37 (3H, d, J=7Hz), 1.9-2.1 (2H, m), 2.26 (3H X1/4,s), 2.30 (3H x 1/4,s), 2.33 (3H x 1/2,s), 2.4-2.6 (4H, m), 2.6-2.8 (4H, m), 2.8-3.0 (2H, m), 3.2-3.3 (2H, m), 3.3-3.5 (2H, m), 3.8-4.2 (2H, m), 4.2-4.3 (2H, m), 4.5-4.6 (1H, m), 5.21 (2H, s), 5.24 (1H, d, J=14Hz), 5.49 (1H, d, J=14Hz), 7.44 (2H, d, J=9Hz), 7.50 (2H, d, J=9Hz), 8.23 (4H, d, J=9Hz).

Example 8.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-2-((7- methyl -3 ,7- diazabicyclo (3.3.0) octane -3-yl) carbonyl) pyrrolidine -4- yl) thio)-1- carba pen -2- em -3- carboxylic acid.

(0208)



(0209)

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -2-((7- methyl -3 ,7- diazabicyclo [3.3.0) octane -3- yl] carbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -4- yl) thio)-1- carba pen -2- em -3- carboxylic acid 4- nitrobenzyl ester (385 mg, 0.494 mmol)) was dissolved in tetrahydrofuran (4.5 ml) - water (4 ml) mixed solvent, and 10 % palladium - carbon catalyst (790 mg) was added and the mixture was stirred at room temperature under hydrogen 1 atmosphere for one hour 30 minutes. The catalyst was eliminated by filtration and the filtrate was diluted with water and was washed with ether. The aqueous layer was concentrated under reduced pressure, and it was subjected to reverse phase column chromatography using Cosmosil C-18PREP (made by Nacalai Tesque Co.) 15 g, and the fraction eluted with acetonitrile - water (5:95-6:94) was recovered, and it was freeze-dried, and the title compound comprising a straw-coloured powder (80 mg, yield 35 %) was thereby obtained.

(0210)

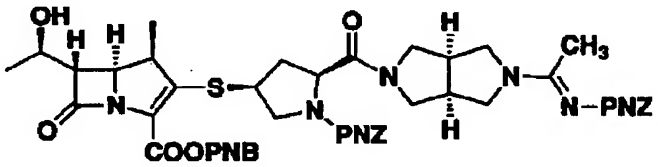
UV spectrum lambda $_{max}$ (H2O):302nm.IR spectrum ν_{max} (KBr) cm^{-1}:3359, 2964, 2872, 2780, 1755, 1640, 1603, 1460, 1386.

NMR spectrum (270 MHz, D2O) δ ppm:1.219 (3H X1/2,d, J=7Hz), 1.223 (3H X1/2,d, J=7Hz), 1.30 (3H, d, J=6Hz), 1.6-1.8 (1H, m), 2.6-2.9 (1H, m), 2.9 (3H, s), 3.06 (1H X1/3,d, J=4Hz), 3.11 (1H x 2/3,d, J=4Hz), 3.1-3.3 (4H, m), 3.2-3.4 (2H, m), 3.43 (1H x 1/2,d, J=6Hz), 3.44 (1H x 1/2,d, J=6Hz), 3.5-4.0 (7H, m), 4.03 (1H x 1/2,d, J=4Hz), 4.10 (1H x 1/2,d, J=4Hz), 4.2-4.3 (2H, m).

Example 9.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-2-((7- (N-(4- nitrobenzyl oxycarbonyl) aceto imidoyl)-3 ,7- diazabicyclo (3.3.0) octane -3- yl) carbonyl) pyrrolidine -4- yl) thio)-1- carbapenem -3- carboxylic acid 4- nitrobenzyl ester.

(0211)



(0212)

(((2S,4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2- yl) carbonyl)-7- (N-(4- nitrobenzyl oxycarbonyl) aceto imidoyl)-3 ,7- diazabicyclo (3.3.0) octane (400 mg, 0.59 mmol)) was dissolved in 75 % methanol - acetonitrile (8 ml), and under a nitrogen atmosphere sodium methoxide solution prepared using metallic sodium (13.5 mg, 0.59 mmol)) and methanol 1.35 ml was added at 0°C. The mixture was stirred at 0°C for 30 minutes, and next, acetic acid (39 mg, 0.65 mmol)) was added, and a solution of (2S,4S)-4- mercapto -2-(7- (N-(4- nitrobenzyl oxycarbonyl) aceto imidoyl)-3 ,7- diazabicyclo (3.3.0) octane -3- yl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine was obtained. Meanwhile, (1R, 3R, 5R, 6S), -6-((R)-1- hydroxyethyl)-1- methyl -2- oxo carba penam -3- carboxylic acid 4- nitrobenzyl ester (255 mg, 0.70 mmol)) was dissolved in dried acetonitrile (8 ml) and diisopropyl ethylamine (100 mg, 0.77 mmol)) and diphenyl chlorophosphate (189 mg, 0.70 mmol)) were added while ice cooling under a nitrogen atmosphere and stirring and the mixture was stirred at the same temperature for 30 minutes. Further diisopropyl ethylamine (100 mg, 0.77 mmol)) was added, and next, the solution of the above obtained (2S, 4S) -4- mercapto -2-(7- (N-(4- nitrobenzyl oxycarbonyl) aceto imidoyl)-3 ,7- diazabicyclo (3.3.0) octane -3- yl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine was added. The liquid mixture was stirred under ice cooling for a further four hours, and next, dilute sodium carbonate solution was added, and extraction with ethyl acetate was carried out. The extract was washed with saturated aqueous sodium chloride solution and is dried (Magnesium sulphate). Next, the residue obtained by concentrating down the solvent under reduced pressurewas subjected to column chromatography silica gel (20 g), and was eluted with a mixed solvent of methanol -50 % ethyl acetate /

methylene chloride (5:95-7:93), and a pale yellow foamed title compound (385 mg, 57 %) was thereby obtained.

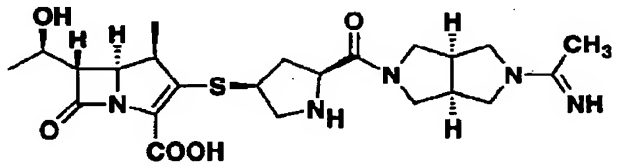
(0213)

IR spectrum ν_{max} (KBr) cm^{-1}:3418,2968,2877,1773,1709,1657,1550,1520,1429,1346.
NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.27 (3H x 1/2,d, J=7.3Hz), 1.28 (3H x 1 /2, d, J :7.3 Hz), 1.36 (3H, d, J :6.4 Hz), 1.67-2.16 (4H, m), 2.21-2.24 (3H, m), 2.56-2.74 (1H, m), 2.87-3.22 (2H, m), 3.28 (1H, dd, J :6.6 Hz, 1.7 Hz), 3.34-4.16 (9H, m), 4.23-4.29 (2H, m), 4.44-4.51 (1H, m), 5.15-5.26 (4H, m), 5.24 (1H, d, J :13.7 Hz), 5.49 (1H, d, J :13.7 Hz), 7.41-7.51 (2H, m), 7.57 (2H, d, J :8.8 Hz), 7.65 (2H, d, J :8.8 Hz), 8.14-8.24 (6H, m).

Example 10.

(1R, 5S, 6S) -2-((2S, 4S) -2-(((7- (aceto imidoyl) -3 ,7- diazabicyclo (3.3.0) octane -3- yl) carbonyl) pyrrolidine -4- yl) thio)-6-((R)-1- hydroxyethyl)-1- methyl carbapenem -3- carboxylic acid.

(0214)



(0215)

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -2-(((7- (N-(4- nitrobenzyl oxycarbonyl) aceto imidoyl)-3 ,7- diazabicyclo (3.3.0) octane -3- yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (300 mg, 0.31 mmol)) was dissolved in a mixed solvent of tetrahydrofuran (4.5 ml) and water (3 ml) and 10 % palladium - carbon (900 mg) was added and the mixture was stirred at room temperature under ambient pressure hydrogen for two hours 30 minutes. The catalyst was eliminated by filtration, and the filtrate was diluted with water, and it was washed twice with ether. The aqueous layer was concentrated under reduced pressure, and the fraction obtained when subjected to reverse phase column chromatography Cosmosil (C-18PREP/ Nacalai Tesque make/30g), and eluted with 2-5 % acetonitrile - water was recovered, and it was freeze-dried, and the title compound of white powdered form (69 mg, 45 %) was thereby obtained.

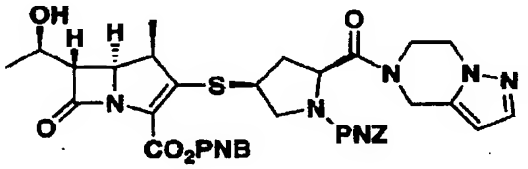
(0216)

IR spectrum ν_{max} (KBr) cm^{-1}:3373,3137,2969,2885,1756,1649,1463,1376.
UV spectrum lambda $_{max}$ (H2O):302nm.
NMR spectrum (270 MHz, D2O) δ ppm:1.21 (3H, d, J=6.8Hz), 1.30 (3H, d, J=6.4Hz), 2.00 (1H, m), 2.28 (3H, d, J=2.4Hz), 3.07 (1H, m), 3.28-3.52 (8H, m), 3.61-3.66 (2H, m), 3.74-4.08 (8H, m), 4.22-4.28 (2H, m).

Example 11.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-1-(4- nitrobenzyl oxycarbonyl) -2-((4,5,6,7- tetrahydropyrazolo (2,3- a) pyrazine -5- yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester.

(0217)



(0218)

(2S, 4S) -4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) -2-((4, 5,6,7- tetrahydropyrazolo (2,3- a) pyrazine -5- yl) carbonyl) pyrrolidine (1034 mg, 2.18 mmol)) was dissolved in methanol (10 ml), and solution of sodium methoxide prepared from metallic sodium (59 mg, 2.56 mmol)) and methanol (2 ml) was added under ice cooling. The mixture was stirred under ice cooling for ten minutes, and next, acetic acid (154 mg, 2.56 mmol)) was added, and solution of (2S, 4S)-4- mercapto -1-(4- nitrobenzyl oxycarbonyl) -2-((4,5,6,7- tetrahydropyrazolo (2,3- a) pyrazine -5- yl) carbonyl) pyrrolidine was obtained. Meanwhile, (1R, 3R, 5R, 6S), -6-((R)-1- hydroxyethyl)-1- methyl -2- oxo carba penam -3- carboxylic acid 4- nitrobenzyl ester (873 mg, 2.40mmol)) was dissolved in acetonitrile (10 ml), and diisopropyl ethylamine (338 mg, 2.62 mmol)) and diphenyl chlorophosphate (704 mg, 2.62 mmol)) were added under ice cooling and the mixture was stirred for one hour, and next, diisopropyl ethylamine (338 mg, 2.62 mmol)) was added once again. This solution was added to the above obtained solution of (2S, 4S) -4- mercapto -1-(4- nitrobenzyl oxycarbonyl) -2-((4,5,6,7- tetrahydropyrazolo (2,3- a) pyrazine -5- yl) carbonyl) pyrrolidine. The mixture was stirred under ice cooling for a further three hours 30 minutes, and next, dilute sodium carbonate solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, and the solvent was eliminated by distillation under reduced pressure, and the residue was subjected to column chromatography using silica gel 30 g, and it was eluted with methanol - ethyl acetate (1:19), and pale yellow foamed title compound (983 mg, yield 82 %) was thereby obtained.

(0219)

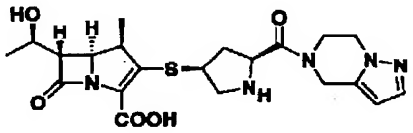
IR spectrum ν_{max} (CHCl3) cm^{-1}:3400,2970,1770,1700,1650,1520,1345.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.26 (3H, d, J=7Hz), 1.34 (3H, d, J=6Hz), 2.6-2.8 (1H, m), 3.2-4.4 (11H, m), 3.27 (1H, dd, J=7, 3Hz), 4.6-5.0 (3H, m), 5.23 (2H, s), 5.25 (1H, d, J=14Hz), 5.50 (1H, d, J=14Hz), 6.10 (1H, brs), 7.50 (1H, brs), 7.52 (2H, d, J=9Hz), 7.67 (2H, d, J=9Hz), 8.21 (4H, d, J=9Hz).

Example 12.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-2-((4, 5,6,7- tetrahydropyrazolo (2,3- a) pyrazine -5-yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid.

(0220)



(0221)

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-1-(4- nitrobenzyl oxycarbonyl) -2-((4,5,6,7- tetrahydropyrazolo (2,3- a) pyrazine -5-yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3-carboxylic acid 4- nitrobenzyl ester (129 mg, 0.166 mmol)) was dissolved in tetrahydrofuran (1ml)-water (1 ml) mixed solvent, and 10 % palladium - carbon catalyst (250 mg) was added and the mixture was stirred at room temperature under ambient pressure / hydrogen for three hours. The catalyst was eliminated by filtration and the filtrate was diluted with water and was washed with ether. The aqueous layer was concentrated under reduced pressure and was subjected to reverse phase column chromatography using Cosmosil C-18PREP (made by Nacalai Tesque) 4.6 g, and the fraction eluted with acetonitrile - water (1:19) was freeze-dried, and the title compound comprising a straw-coloured powder (50 mg, yield 65 %) was thereby obtained.

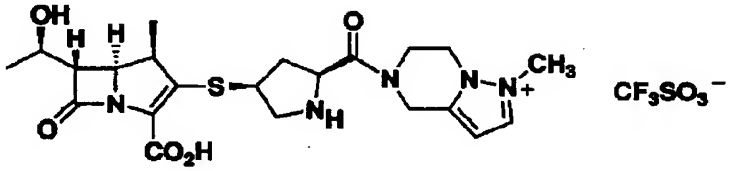
(0222)

IR spectrum ν_{max} (KBr) cm^{-1}:3396,2969,1755,1657,1595,1488,1453,1387,1259,1183,1136,1094,775.
NMR spectrum (270 MHz, D2O) δ ppm:1.18 (3H x (1/2), d, J=7Hz), 1.21 (3H x (1/2), d, J=6Hz), 1.29 (3H, d, J=6Hz), 1.93 (1H X(1/2), dt, J=14,7Hz), 2.01 (1H x (1/2), dt, J=14, 7Hz), 2.9-3.2 (1H, m), 3.34 (1H, quintet, J=7Hz), 3.44 (1H, dd, J=12, 5Hz), 3.47 (1H, dd, J=6, 2Hz), 3.69 (1H, ddd, J=12, 6, 2Hz), 4.0-4.1 (1H, m), 4.03 (2H, t, J=6Hz), 4.1-4.3 (4H, m), 4.8-5.0 (1H, m), 4.89 (2H, s), 6.29 (1H, br.s), 7.70 (1H, br.s).

Example 13.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-2-((1- methyl -4, 5,6,7- tetrahydro -1 ,6-di aza -7 a- azonia -1H- indene -5-yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid trifluoromethanesulfonate.

(0223)



(0224)

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-1-(4- nitrobenzyl oxycarbonyl) -2-((4,5,6,7- tetrahydropyrazolo (2,3- a) pyrazine -5- yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3-carboxylic acid 4- nitrobenzyl ester (110 mg, 0.14 mmol)) was dissolved in acetonitrile (1 ml), and trifluoromethanesulfonic acid methyl ester (23 mg, 0.14 mmol)) was added under ice cooling, and the mixture was stirred at room temperature for one hour. The solvent was eliminated by distillation under reduced pressure, and the residue was dissolved in tetrahydrofuran (1.0 ml) - water (0.8 ml) mixed solvent, and 10 % palladium - carbonic acid catalyst (245 mg) was added and the mixture was stirred at room temperature under ambient pressure / hydrogen for three hours. The catalyst was eliminated by filtration and the filtrate was diluted with water and was washed with ether. The aqueous layer was concentrated under reduced pressure and was submitted to reverse phase column chromatography using Cosmosil C-18PREP (made by Nacalai Tesque) 4.6 g, and the fraction eluted with acetonitrile - water (3:47) was freeze-dried, and the title compound comprising a straw-coloured powder (35 mg, yield 39 %) was thereby obtained.

(0225)

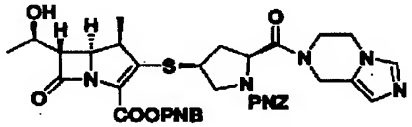
IR spectrum ν_{max} (KBr) cm^{-1}:3397,2968,1753,1656,1597,1385,1264,1031,639.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.21 (3H x (1/2), d, J=7Hz), 1.22 (3H x (1/2), d, J=7Hz), 1.30 (3H, d, J=6Hz), 1.7-1.9 (1H, m), 2.7-3.0 (1H, m), 3.18 (1H, dt, J=12, 4Hz), 3.3-3.4 (1H, m), 3.30 (1H, quintet, J=7Hz), 3.45 (1H, dd, J=7, 3Hz), 3.8-4.0 (1H, m), 4.09 (3H, s), 4.1-4.3 (3H, m), 4.3-4.6 (3H, m), 4.8-5.0 (1H, signal and duplication of water -d1), 5.03 (2H, s), 6.72 (1H, brs), 8.17 (1H, br.s).

Example 14.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -1-(4- nitrobenzyl oxycarbonyl) -2-(5,6,7,8- tetrahydroimidazo (1,5- a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3-carboxylic acid 4- nitrobenzyl ester.

(0226)



(0227)

To methanol (20 ml) solution of (2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) -2- (5,6,7,8-tetrahydroimidazo (1,5-a) pyrazine-7-ylcarbonyl) pyrrolidine (1.50 g, 3.17 mmol)), was added methanol (1.5 ml) solution of metallic sodium (73 mg, 3.2 mmol)) under ice cooling and the mixture was stirred for five minutes. On completion of the reaction, 0.1 M phosphoric acid buffer (pH7.4, 20ml) and water (10 ml) were added, and extraction was carried out with ethyl acetate. The organic layer was dried with anhydrous magnesium sulphate, and next it was concentrated. The obtained residue and (1R, 5R, 6S) -6-

((R)-1- hydroxyethyl)-1- methyl -2- (diphenylphosphoryl oxy) carbapenem -3- carboxylic acid 4-nitrobenzyl ester (1.78 g, 2.99 mmol)) was dissolved in acetonitrile (25 ml), and diisopropyl ethylamine (0.52 ml, 3.0 mmol)) was added under ice cooling and was stirred at 0-10°C for 16 hours. On completion of the reaction, it was diluted with ethyl acetate, and next, it was washed with water, saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution. The organic layer was dried with anhydrous sodium sulphate, and it was concentrated, and next, it was refined by column chromatography (development solvent : dichloromethane - ethyl acetate - methanol (1:0:0-0:1-3:6:1)) using silica gel, and the title compound (965 mg) was obtained as a straw-coloured powder.

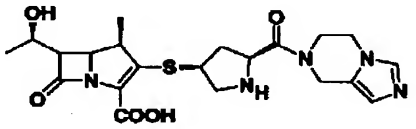
(0228)

IR spectrum ν_{max} (KBr) cm^{-1}:3415,3115,2971,2938,2876,1769,1705,1657,1607.
NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.22-1.30 (3H, m), 1.37 (3H, d, J=6.1Hz), 1.85-2.05 (1H, m), 2.65-2.85 (1H, m), 3.28 (1H, dd, J=7.0, 2.5Hz), 3.30-4.30 (10H, m), 4.55-5.00 (4H, m), 5.20 (2H, s), 5.20-5.52 (2H, m), 6.89 (1H, s), 7.35 (1H, s), 7.40-7.66 (4H, m), 8.12, 8.21 (4H, dX2,J=8.6Hz).

Example 15.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((1S, 4S) -2-(5, 6,7,8- tetrahydroimidazo (1,5- a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid.

(0229)



(0230)

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -1-(4- nitrobenzyl oxycarbonyl) -2-(5,6,7,8-tetrahydroimidazo (1,5-a) pyrazine-7-ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3-carboxylic acid 4- nitrobenzyl ester (150 mg, 1.93 x 10^{-4}mol)) was dissolved in water - tetrahydrofuran (1:1) mixed solvent (3 ml), and 10 % Pd-C (200 mg) was added under a stream of nitrogen. The reaction container interior was purged with hydrogen and next, the mixture was stirred at room temperature under ambient pressure / hydrogen for 1.2 hours. The reaction liquid was filtered, and it was diluted with water (about 30 ml), and next, it was washed three times with ether (30 ml). The aqueous layer was concentrated to about 5 ml and was refined with reverse-phase chromatography (development solvent : water - acetonitrile (1:0)-(95:5)). Freeze-drying was carried out, and the title compound (39.5 mg) was obtained as a colourless cotton-like material.

(0231)

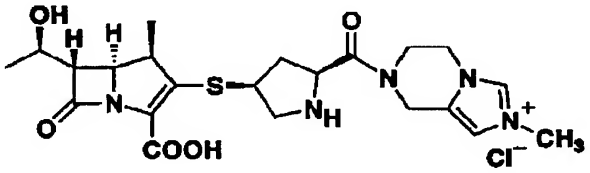
IR spectrum ν_{max} (KBr) cm^{-1}:3410,2971,1765,1649,1595.
NMR spectrum (270 MHz, D2O) δ ppm:1.17-1.25 (3H, m), 1.30 (3H, d, J=6.3Hz), 1.70-1.86 (1H, m),

2.84-2.95 (1H, m), 3.23 (1H, dd, J=12.2, 3.9Hz), 3.31-3.46 (3H, m), 3.86-3.97 (2H, m), 3.99-4.04 (1H, m), 4.17-4.30 (4H, m), 4.46 (1H, dd, J=8.8, 7.3Hz), 4.83, 4.85 (2H, s X2), 6.93, 6.95 (1H, s X2), 7.77, 7.80 (1H, s X2).

Example 16.

7-((2S, 4S) -4-((1R, 5S, 6S) -3- carboxy -6-((R)-1- hydroxyethyl)-1- methyl carbapenem -2- ylthio) pyrrolidine -2- ylcarbonyl)-2- methyl -5, 6,7,8- tetrahydroimidazo (1,5- a) pyrazinium chloride.

(0232)



(0233)

Trifluoromethanesulfonic acid methyl ester (0.16 ml, 1.4 mmol)) was added at room temperature to acetonitrile (20 ml) solution of (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S,4S)-1-(4-nitrobenzyl oxycarbonyl) -2-(5,6,7,8- tetrahydroimidazo (1,5- a) pyrazine -7- ylcarbonyl) pyrrolidine -4-ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (1.00 g, 1.29 x 10^{-3}mol)) and the mixture was stirred for 30 minutes. The reaction liquid was concentrated, and the residue was washed with ether. The obtained straw-coloured solid was dissolved in a mixed solvent of tetrahydrofuran (8 ml) and water (6 ml), and 10 % Pd-C (600 mg) was added under a stream of nitrogen. The reaction container interior was purged with hydrogen and the mixture was stirred at room temperature under ambient pressure / hydrogen for four hours. On completion of the reaction, it was filtered, and it was diluted with water (about 50 ml), and next, it was washed twice with ether (about 50 ml). The aqueous layer was concentrated to about 10 ml and was passed through ion exchange resin (Dowex1-4XCl form, 20 ml). The obtained fraction was concentrated to around 10 ml again, and it was subjected to reverse-phase chromatography (eluent : water) and was purified. Freeze-drying was carried out, and the title compound (210 mg) was obtained as a colourless cotton-like material.

(0234)

IR spectrum ν_{max} (KBr) cm^{-1}:3420,2971,1754,1657,1597.

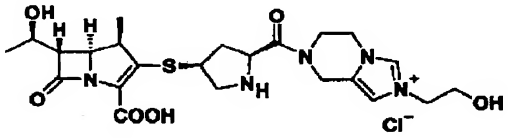
NMR spectrum (270 MHz, D2O) δ ppm:1.21, 1.22 (3H, d X2,J=7.3Hz), 1.29 (3H, t, J=5.4Hz), 1.95-2.10 (1H, m), 3.03-3.17 (1H, m), 3.32-3.44 (1H, m), 3.46-3.53 (2H, m), 3.78 (1H, dd, J=12.2, 6.3Hz), 3.89, 3.91 (3H, s X2), 4.01-4.46 (7H, m), 4.66-5.00 (3H, m), 7.33, 7.40 (1H, s X2), 8.70, 8.75 (1H, s X2).

Example 17.

7-((2S, 4S) -4-((1R, 5S, 6S) -3- carboxy -6-((R)-1-1- hydroxyethyl)-1- methyl carbapenem -2- ylthio)

pyrrolidine -2- ylcarbonyl)-2-(2- hydroxyethyl) -5, 6,7,8- tetrahydroimidazo (1,5- a) pyrazinium chloride.

(0235)



(0236)

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -1-(4- nitrobenzyl oxycarbonyl) -2-(5,6,7,8-tetrahydroimidazo (1,5-a) pyrazine-7-ylcarbonyl) carbapenem -3- carboxylic acid 4-nitrobenzyl ester (960 mg, 1.24 mmol)) and iodo ethanol (2.0 g, 1.1 X10-2mol)) was dissolved in acetonitrile (5 ml) and the mixture stirred at 60°C for five hours. The reaction liquid was concentrated, and the residue was washed with isopropyl ether. The obtained residue was sjubject to a deprotecting reaction, ion exchange, purification and freeze drying in the same way as the earlier described compounds, and the title compound (190 mg) was thereby obtained as a colourless cotton-like material.

(0237)

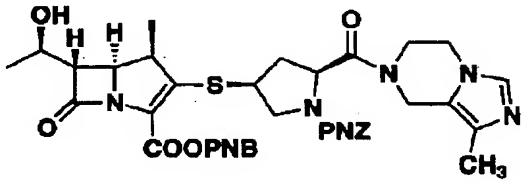
IR spectrum ν_{max} (KBr) cm^{-1}:3389,3133,2968,1755,1660,1600,1559.

NMR spectrum (270 MHz, D2O) δ ppm:1.19-1.22 (3H, m), 1.29 (3H, d, J=6.3Hz), 1.98-2.10 (1H, m), 3.06-3.17 (1H, m), 3.33-3.42 (1H, m), 3.47 (1H, dd, J=5.9, 2.5Hz), 3.52 (1H, dd, J=12.3, 5.0Hz), 3.81 (1H, dd, J=12.3, 6.3Hz), 3.94 (2H, t, J=4.9Hz), 4.02-4.30 (4H, m), 4.34 (2H, t, J=4.9Hz), 4.35-4.50 (2H, m), 4.70-4.99 (4H, m), 7.50 (1H, s), 8.87 (1H, s).

Example 18.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -2-(1- methyl -5, 6,7,8- tetrahydroimidazo (1,5- a) pyrazine -7- ylcarbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -4- ylthio) carbapenem -3-carboxylic acid 4- nitrobenzyl ester.

(0238)



(0239)

(2S, 4S)-4-(4- methoxybenzyl thio) -2-(1- methyl -5, 6,7,8- tetrahydroimidazo (1,5- a) pyrazine -7-ylcarbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine (130 mg, 2.30X10-4 mol)) was dissolved in a mixed solvent of trifluoroacetic acid (1.2 ml) and anisole (0.24 ml). Trifluoromethanesulfonic acid (20 μl) was added at room temperature and the mixture was stirred for three hours.

On completion of the reaction, it was azeotroped twice with 1,2- dichloromethane, and the obtained residue was washed successively with hexane and ether. This residue and (1R, 5R, 6 R) -6-((R)-1-hydroxyethyl)-1- methyl -2- (diphenylphosphoryl oxy) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (150 mg, 2.52 X10-4mol)) were dissolved in acetonitrile (about 10 ml), and diisopropyl ethylamine (200 μl, 1.15 X 10^{-3} mol)) was added under ice cooling, and the mixture was left to stand at 0-4°C for 12 hours. The reaction liquid was concentrated, and the obtained residue was dissolved in the ethyl acetate which contained methanol 5 %, and it was washed with water.
The organic layer was dried, and next, it was concentrated, and the residue was refined with column chromatography (development solvent : ethyl acetate - methanol (1:0)-(9:1)) using alumina, and the title compound (120 mg) was obtained as straw-coloured foamed substance.

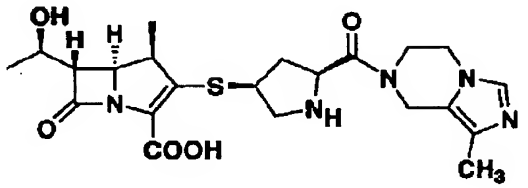
(0240)

IR spectrum ν_{max} (KBr) cm^{-1}:3400,3113,3080,2969,2873,1772,1709,1660,1607.
NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.27 (3H, d, J=7.3Hz), 1.37 (3H, d, J=6.3Hz), 1.85-2.05 (1H, m), 2.21 (3H, brs), 2.65-2.85 (1H, m), 3.28 (1H, dd, J=6.8, 2.4Hz), 3.30-3.45 (1H, m), 3.47-3.60 (1H, m), 3.65-4.30 (12H, m), 4.50-5.10 (3H, m), 5.20 (2H, s), 5.23 (1H, d, J=14.2Hz), 5.47 (1H, d, J=14.2Hz), 7.36, 7.43 (1H, s X2), 7.50 (2H, d, J=8.8Hz), 7.65 (2H, d, J=8.8Hz), 8.23 (4H, d, J=8.8Hz).

Example 19.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -2-(1- methyl -5, 6,7,8- tetrahydroimidazo (1,5- a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid.

(0241)



(0242)

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -2-(1- methyl -5, 6,7,8- tetrahydroimidazo (1,5- a) pyrazine -7- ylcarbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -4- ylthio) carbapenem -3-carboxylic acid 4- nitrobenzyl ester (120 mg, 1.54 X10-4mol)) was dissolved in a mixed solvent of tetrahydrofuran - water (1:1) (2 ml), and 10 % Pd-C (150 mg) was added. Under ambient pressure / hydrogen, the mixture was stirred at room temperature for two hours. The reaction liquid was filtered, and it was diluted with water, and next, it was washed three times with ether. The aqueous layer was concentrated to about 5 ml and it was subjected to reverse phase column chromatography (development solvent : water - acetonitrile (1:0)-(9:1)) and was refined. Freeze-drying was carried out, and the title compound (17.0 mg) was obtained as a colourless cotton-like material.

(0243)

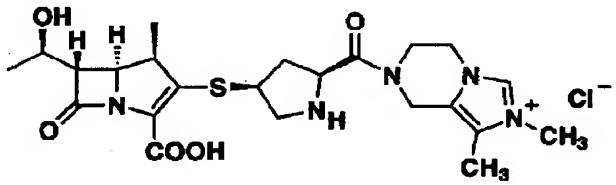
IR spectrum ν_{max} (KBr) cm^{-1}:3385,2969,2929,2869,2497,1754,1651,1596.

NMR spectrum (270 MHz, D2O) δ ppm:1.26 (3H, d, J=7.3Hz), 1.30 (3H, d, J=6.4Hz), 1.63-1.83 (1H, m), 2.15 (3H, s), 2.85 (1H, dt, J=14.2, 8.3Hz), 3.17 (1H, dd, J=12.2, 3.9Hz), 3.25-3.46 (3H, m), 3.83-4.10 (3H, m), 4.12-4.45 (5H, m), 4.60-4.90 (4H, m), 7.75, 7.79 (1H, sX2).

Example 20.

7-((2S, 4S) -4-((1R, 5S, 6S) -3- carboxy -6-((R)-1- hydroxyethyl)-1- methyl carbapenem -2- ylthio) pyrrolidine -2- ylcarbonyl)-1 ,2- dimethyl -5, 6,7,8- tetrahydroimidazo (1,5- a) pyrazinium chloride.

(0244)



(0245)

Trifluoromethanesulfonic acid methyl ester (25 μl, 2.2 X10-4mol)) was added at room temperature to acetonitrile (3 ml) solution of (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-2-(1-methyl -5,6,7,8- tetrahydroimidazo (1,5-a) pyrazine -7- ylcarbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (160 mg, 2.02 X10-4mol)) and, for 30 minutes, was stirred at the same temperature. The reaction liquid was concentrated, and the residue was washed with hexane and ethyl acetate, and after drying, was dissolved in water - tetrahydrofuran (1:1) mixed solvent (3 ml). 10 % Pd-C (300 mg) was added under a stream of nitrogen, and next, the reaction liquid was stirred at room temperature under ambient pressure / hydrogen for one hour 30 minutes. The reaction liquid was filtered, and it was diluted with water, and next, it was concentrated to about 5 ml.

This concentrated liquid was passed through ion exchange resin (Dowex1-4X Cl form, 6 ml). The obtained fraction was concentrated to around 5 ml again and was submitted to reverse-phase chromatography (development solvent : water) and was thereby refined. Freeze-drying was carried out, and the title compound (18.5 mg) was obtained as a colourless cotton-like material.

(0246)

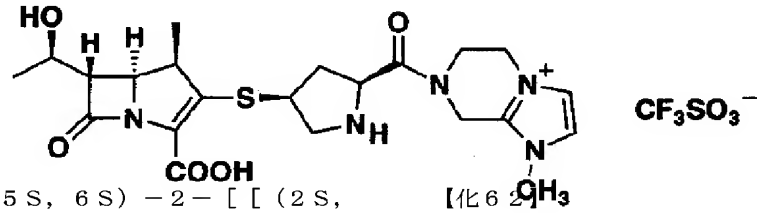
IR spectrum ν_{max} (KBr) cm^{-1}:3399,3141,2968,1758,1661,1601,1564.

NMR spectrum (270 MHz, D2O) δ ppm:1.20,1.21 (3H, d X2, J :7.3 Hz), 1.29 (3H, d, J :6.3 Hz), 1.96-2.11 (1H, m), 2.26 (3H, s), 3.04-3.19 (1H, m), 3.30-3.43 (1H, m), 3.47 (1H, dd, J :5.9, 2.4 Hz), 3.52 (1H, dd, J :12.2, 4.9 Hz), 3.78 (3H, s), 3.78-3.85 (1H, m), 3.96-4.00 (1H, m), 4.03-4.16 (2H, m), 4.18-4.42 (4H, m), 4.50-4.98 (3H, m), 8.66 (1H, s).

Example 21.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-2-((1- methyl -4, 5,6,7- tetrahydro -1 ,6- di aza -3 a- azonia -1H- indene -6-yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid trifluoromethanesulfonate.

(0247)



R, 5S, 6S) −2− [[(2S, [化62]

(0248)

(1R, 5S, 6S) -2-(((2S,4S)-2- (N-(2- hydroxyethyl) -N-((1- methyl -2- imidazolyl) methyl) carbamoyl)-1- (4- nitrobenzyl oxycarbonyl) pyrrolidine -4- yl) thio)-6-((R)-1- hydroxyethyl)-1- methyl carbapenem -3- carboxylic acid 4- nitrobenzyl ester (195 mg, 0.24 mmol)) was dissolved in acetonitrile (2 ml), and pyridine (36 mg, 0.45 mmol)) and anhydrous trifluoromethanesulfonic acid (75 mg, 0.26 mmol)) were added under ice cooling. The mixture was stirred under ice cooling for one hour 30 minutes, and next, it was diluted with ethyl acetate, and it was washed with water. The solvent was eliminated by distillation under reduced pressure, and the residue was subjected to reverse phase column chromatography using CHP-20P8g, and the fraction eluted with acetonitrile - water (4:6) was concentrated under reduced pressure, and the residue comprising a straw-coloured powder (169 mg) was obtained.

This was dissolved in tetrahydrofuran (2ml)- water (2 ml) mixed solvent, and 10 % palladium - carbon catalyst (450 mg) was added and the mixture was stirred at room temperature under ambient pressure / hydrogen for three hours 30 minutes. The catalyst was eliminated by filtration and the filtrate was diluted with water and was washed with ether. The aqueous layer was concentrated under reduced pressure, and it was subjected to the reverse phase column chromatography which used Cosmosil C-18PREP (made by Nacalai Tesque) 4.6 g, and the fraction eluted with acetonitrile - water (1:99) was freeze-dried, and the title compound comprising a straw-coloured powder (15 mg, yield 10 %) was thereby obtained.

(0249)

UV spectrum lambda $_{max}$ (H2O):300nm.

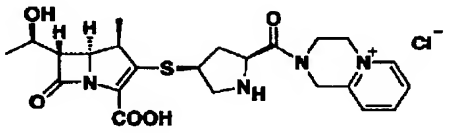
IR spectrum ν_{max} (KBr) cm^{-1}:3414,2970,1756,1668,1599,1384,1278,1261,1227,1160,1031,639.

NMR spectrum (270 MHz, D2O) δ ppm:1.02 (3H, d, J=7Hz), 1.09 (3H, d, J=6Hz), 1.88 (1H, dt, J=14, 7Hz), 2.94 (1H, dt, J=14, 7Hz), 3.18 (1H, dq, J=9, 7Hz), 3.28 (1H, dd, J=6, 3Hz), 3.32 (1H, dd, J=12, 5Hz), 3.61 (3H, s), 3.8-4.0 (2H, m), 4.05 (1H, dd, J=9, 3Hz), 4.07 (1H, quintet, J=6Hz), 4.1-4.2 (2H, m), 4.78 (1H, t, J=7Hz), 4.89 (2H, s), 7.28 (2H, s).

Example 22.

2-((2S, 4S) -4-((1R, 5S, 6S) -3- carboxy -6-((R)-1- hydroxyethyl)-1- methyl carbapenem -2- ylthio) pyrrolidine -2- ylcarbonyl) pyrido (1,2- a)-1, 2,3,4- tetrahydro pyrazinium chloride)

(0250)



(0251)

Anhydrous trifluoromethanesulfonic acid (208 μl, 1.24 mmol)) was added under ice cooling to acetonitrile (15 ml) solution of (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-2-((2S, 4S) -2- (N-(2-hydroxyethyl) - (N-[2- pyridyl] methyl) carbamoyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -4-ylthio)-1- methyl carbapenem -3- carboxylic acid -4- nitrobenzyl ester (910 mg, 1.13 mmol)) and pyridine (0.20 ml, 2.5 mmol)) and the mixture was stirred for 15 minutes. The reaction liquid was diluted with ethyl acetate (50 ml) and next, was washed with water twice with saturated aqueous sodium bicarbonate solution (30 ml). The organic layer was dried with anhydrous magnesium sulphate, and next it was concentrated, and the residue was dissolved in water - tetrahydrofuran 1:1 mixed solvent (18 ml). 10 % Pd-C (900 mg) was added under a stream of nitrogen to reaction solution, and the reaction container interior was purged with hydrogen and the mixture was stirred at ordinary temperature and normal pressure for three hours. The reaction mixture liquid was diluted with water (150 ml) after filtration, and it was washed three times with ether (100 ml). The aqueous layer was concentrated under reduced pressure to about 15 ml and was passed through column of ion exchange resin (Dowex1-X4,Cl form, 20 ml). The obtained fraction was concentrated to about 15 ml and was refined by the column chromatography using a reverse phase column (development solvent : water), and freeze-drying was performed, and the target compound comprising a straw-coloured powder (136 mg) was thereby obtained.

(0252)

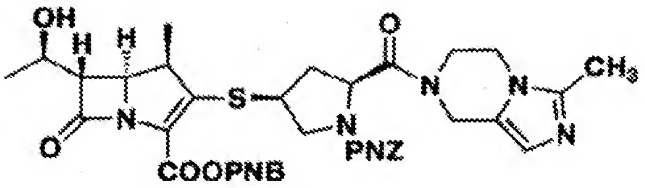
IR spectrum ν_{max} (KBr) cm^{-1}:3450,2960,1750,1660.

NMR spectrum (270 MHz, D2O) δ ppm:1.04 (3H, d, J=7.3Hz), 1.10 (3H, d, J=6.4Hz), 1.80-2.00 (1H, m), 2.85-3.10 (1H, m), 3.15-3.40 (3H, m), 3.60-3.75 (1H, m), 3.85-4.15 (5H, m), 4.65-4.85 (3H, m), 4.95-5.15 (2H, m), 7.80-7.95 (2H, m), 8.35-8.45 (1H, m), 8.60-8.70 (1H, m).

Example 23.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -2-(3- methyl -5, 6, 7, 8-tetrahydroimidazo (1,5- a) pyrazine -7- ylcarbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -4-ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester.

(0253)



(0254)

The title crude compound (1.34 g) was obtained as yellow foamed substance from (2S, 4S)-4- acetylthio -2-(1- methylimidazo (1,5- a)-5, 6, 7, 8- tetrahydro pyrazine -7-yl- carbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine (900 mg, 1.84 mmol) by the same procedures as in Example of (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -1-(4- nitrobenzyl oxycarbonyl) -2- (5,6,7,8-tetrahydroimidazo (1,5-a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester synthesis.

(0255)

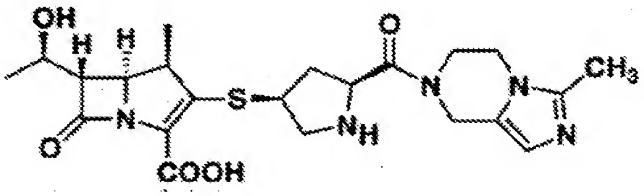
IR spectrum ν_{max} (CHCl3) cm^{-1}:3350,2960,1770,1700,1655,1610.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.28 (3H, d, J=7.5Hz), 1.37 (3H, d, J=6.6Hz), 1.80-2.05 (1H, m), 2.35 (3H, brs), 2.65-2.85 (1H, m), 3.28 (1H, dd, J=7.3, 2.6Hz), 3.30-4.30 (10H, m), 4.55-5.00 (4H, m), 5.22 (2H, brs), 5.20-5.55 (2H, m), 6.74, 6.75 (1H, brsX2), 7.45-7.68 (4H, m), 8.00-8.28 (4H, m).

Example 24.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -2-(3- methyl -5, 6, 7, 8-tetrahydroimidazo (1,5- a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid.

(0256)



(0257)

The title compound (23 mg) was obtained as a colourless cotton-like material from (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -2-(1- methylimidazo (1,5- a)-5, 6, 7, 8- tetrahydro pyrazine -7-yl carbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid 4-nitrobenzyl ester (120 mg, 1.52 $X10^{-4}$ mol) in the same way as in the Example of (1R, 5S, 6S) -5-((R)-1-hydroxyethyl)-1- methyl -2-((2S, 4S) -2- (5,6,7,8-tetrahydroimidazo (1,5-a) pyrazine-7-ylcarbonyl)

pyrrolidine-4-ylthio)) carbapenem -3- carboxylic acid synthesis.

(0258)

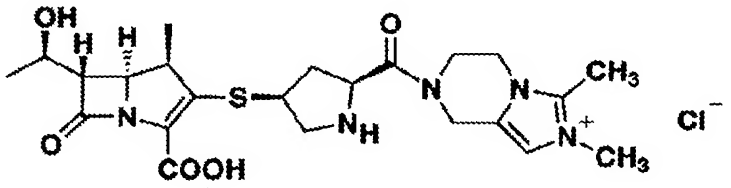
IR spectrum ν_{max} (KBr) cm^{-1}:3371,3141,2968,1756,1660,1596.

NMR spectrum (270 MHz, D2O) δ ppm:1.19, 1.22 (3H, d X2,J=7.3Hz), 1.30 (3H, d, J=6.6Hz), 1.86-2.00 (1H, m), 2.54, 2.56 (3H, sX2), 2.96-3.06 (1H, m), 3.35-3.42 (2H, m), 3.45-3.48 (1H, m), 3.63 (1H, dd, J=12.6, 6.6Hz), 3.97-4.28 (7H, m), 4.65-4.95 (3H, m), 7.17, 7.19 (1H, sX2).

Example 25.

7-((2S, 4S) -4-((1R, 5S, 6S) -3- carboxy -6-((R)-1- hydroxyethyl)-1- methyl carbapenem -2- ylthio) pyrrolidine -2- ylcarbonyl)-2 ,3- dimethyl -5, 6, 7, 8- tetrahydroimidazo (1,5- a) pyrazinium chloride)

(0259)



(0260)

The title compound (260 mg) was obtained as a colourless cotton-like material from (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -2-(3- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- yl) carbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (1.29 g, 1.63 mmol) using the same procedures as in the Example of the synthesis of 7-((2S, 4S) -4-((1R, 5S, 6S) -3- carboxy -6-((R)-1- hydroxyethyl)-1- methyl carbapenem -2- ylthio) pyrrolidine -2- ylcarbonyl)-2- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazinium chloride.

(0261)

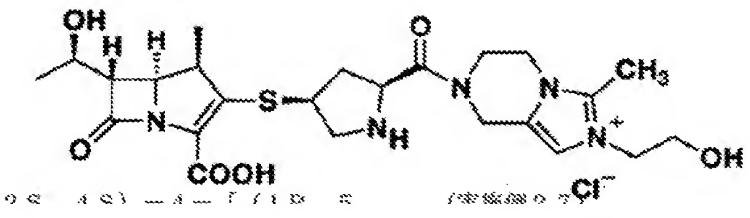
IR spectrum ν_{max} (KBr) cm^{-1}:3390,3119,2966,2741,1755,1661,1601.

NMR spectrum (270 MHz, D2O) δ ppm:1.20, 1.22 (3H, t X3,J=7.3Hz), 1.29 (3H, t, J=6.4Hz), 1.94-2.10 (1H, m), 2.58 (3H, s), 2.98-3.18 (1H, m), 3.30-3.45 (1H, m), 3.47-3.53 (2H, m), 3.70-3.90 (1H, m), 3.78 (3H, s), 4.00-4.15 (3H, m), 4.20-4.33 (4H, m), 4.55-4.95 (3H, m), 7.28 (1H, brs).

Example 26.

7-((2S, 4S) -4-((1R, 5S, 6S) -3- carboxy -6-((R)-1- hydroxyethyl)-1- methyl carbapenem -2- ylthio) pyrrolidine -2- ylcarbonyl)-2-(2- hydroxyethyl) -3- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazinium chloride.

(0262)



(0263)

The title compound (16 mg) was obtained as a colourless cotton-like material from (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -2-(3- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (150 mg, 1.90 x 10^{-4}mol) using the same procedures as in the Example of the synthesis of 7-((2S, 4S) -4-((1R,5S,6S)-3- carboxy -6-((R)-1- hydroxyethyl)-1- methyl carbapenem -2-ylthio) pyrrolidine -2- ylcarbonyl)-2-(2- hydroxyethyl) -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazinium chloride.

(0264)

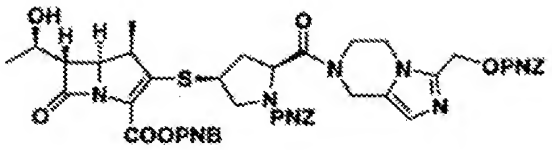
IR spectrum ν_{max} (KBr) cm^{-1}:3353,2966,2930,1757,1661,1600.

NMR spectrum (270 MHz, D2O) δ ppm:1.20, 1.21 (3H, d X2,J=7.3Hz), 1.29 (3H, d, J=6.5Hz), 1.95-2.12 (1H, m), 2.62 (3H, s), 3.03-3.19 (1H, m), 3.30-3.44 (1H, m), 3.45-3.54 (3H, m), 3.80 (1H, dd, J=12.2, 6.3Hz), 3.92 (2H, t, J=5.1Hz), 4.00-4.18 (3H, m), 4.20-4.35 (5H, m), 4.50-4.98 (3H, m), 7.39 (1H, s).

Example 27.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -1-(4- nitrobenzyl oxycarbonyl) -2-(3- (4-nitrobenzyl oxycarbonyl oxy) methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester.

(0265)



(0266)

The title compound (759 mg) was obtained as yellow foamed substance from (2S, 4S)-4- acetylthio -1- (4- nitrobenzyl oxycarbonyl) -2-(3- (4- nitrobenzyl oxycarbonyl oxy) methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine (1.18 g) using the same procedures as in the Example of the synthesis of (1R, 5S, 6S)-6-((R)-1- hydroxyethyl)-1- methyl -2-((2S,4S) -1-(4- nitrobenzyl oxycarbonyl) -2- (5,6,7,8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester.

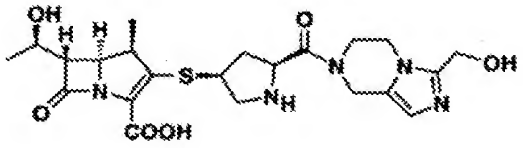
(0267)

IR spectrum ν_{max} (KBr) cm^{-1}:3403,3114,3080,2969,2874,1772,1710,1662,1607.NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.20-1.30 (3H, m), 1.37 (3H, t, J=6.2Hz), 1.85-2.05 (1H, m), 2.65-2.85 (1H, m), 3.25-3.37 (2H, m), 3.45-3.60 (1H, m), 3.65-4.35 (9H, m), 4.55-5.05 (7H, m), 5.21 (2H, brs), 5.15-5.55 (2H, m), 6.77, 6.82 (1H, s X2), 7.30-7.66 (6H, m), 7.95-8.25 (6H, m).

Example 28.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-2-((2S, 4S) -2-(3- (hydroxyethyl) -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio)-1- methyl carbapenem -3- carboxylic acid.

(0268)



(0269)

The title compound (18 mg) was obtained as a colourless cotton-like material from (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S) -1-(4- nitrobenzyl oxycarbonyl) -2-(3- (4- nitrobenzyl oxycarbonyl oxy) methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (160 mg, 1.98 X10-4mol) using the same procedures as in the Example of the synthesis of (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S,4S) -2- (5,6,7,8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio)

carbapenem -3- carboxylic acid.

(0270)

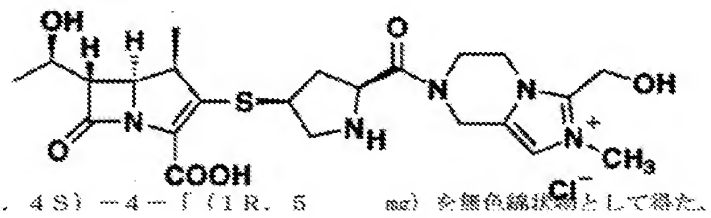
IR spectrum ν_{max} (KBr) cm^{-1}:3349,2967,2931,2869,1749,1641,1603.

NMR spectrum (270 MHz, D2O) δ ppm:1.18, 1.21 (3H, d X2,J=7.3Hz), 1.30 (3H, d, J=6.4Hz), 1.55-1.73 (1H, m), 2.71-2.84 (1H, m), 3.08 (1H, brd, J=12.2Hz), 3.18 (1H, dd, J=12.2, 5.4Hz), 3.33-3.45 (2H, m), 3.76-3.88 (1H, m), 3.96-4.12 (2H, m), 4.15-4.30 (2H, m), 4.66 (2H, d, J=1.5Hz), 4.55-5.00 (3H, m), 6.86 (1H, d, J=1.5Hz).

Example 29.

7-((2S, 4S)-4-((1R, 5S, 6S) -3- carboxy -6-((R)-1- hydroxyethyl)-1- methyl carbapenem -2- ylthio) pyrrolidine -2- ylcarbonyl)-3- (hydroxymethyl) -2- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazinium chloride.

(0271)



(0272)

The title compound (218 mg) was obtained as a colourless cotton-like material using (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-1-(4- nitrobenzyl oxycarbonyl) -2-(3- (4- nitrobenzyl oxycarbonyl oxy) methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (750 mg, 7.70 mmol) using the same procedures as in the Example of the synthesis of 7-((2S, 4S)-4-((1R, 5S,6S)-3- carboxy -6-((R)-1- hydroxyethyl)-1- methyl carbapenem -2- ylthio) pyrrolidine -2- ylcarbonyl)-2- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazinium chloride.

(0273)

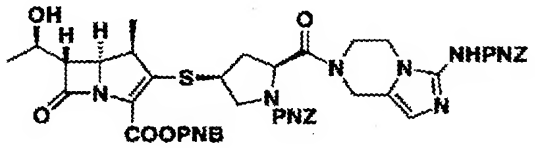
IR spectrum ν_{max} (KBr) cm^{-1}:3388,2967,1755,1661,1598.

NMR spectrum (270 MHz, D2O) δ ppm:1.19-1.22 (3H, m), 1.29 (3H, d, J=6.5Hz), 1.97-2.10 (1H, m), 3.05-3.17 (1H, m), 3.33-3.42 (1H, m), 3.45-3.50 (1H, m), 3.51 (1H, dd, J=12.2, 4.9Hz), 3.80 (1H, dd, J=12.2, 6.4Hz), 3.92 (3H, s), 4.04-4.13 (2H, m), 4.18-4.48 (4H, m), 4.93 (2H, s), 4.70-4.98 (4H, m), 7.41 (1H, s).

Example 30

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-1-(4- nitrobenzyl oxycarbonyl) -2-(3- (4- nitrobenzyl oxycarbonyl) amino -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine -2- ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester.

(0274)



(0275)

Pivaloyl chloride (370 μl, 3.00 mmol)) was added to dichloromethane (25 ml) suspension of (2S, 4S)-4-acetylthio -1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2- carboxylic acid potassium salt (1.22 g, 3.00 mmol)) and the mixture was stirred at room temperature for 30 minutes.

Triethylamine (1.05 ml, 7.53 mmol)) and 3-(4- nitrobenzyl oxycarbonyl) amino -5, 6, 7, 8-tetrahydroimidazo (1, 5-a) pyrazine / dihydrochloride (900 mg, 2.30 mmol)) were added to this reaction liquid and the mixture wa stirred at room temperature for one hour. It was concentrated under reduced pressure, and it was diluted with ethyl acetate (150 ml), and next, it was washed twice with water (100 ml), and it was washed respectively with saturated aqueous sodium bicarbonate solution (100 ml) and saturated aqueous sodium chloride solution (100 ml). The organic layer which was dried on anhydrous magnesium sulphate was concentrated under reduced pressure, and the residue was subjected to short column (development solvent : ethyl acetate - methanol (9:1)) using silica gel, and the polar impurities were removed. The obtained fraction was concentrated under reduced pressure, and the residue was dissolved in a mixed solvent of methanol - acetonitrile (2:1) (30 ml). Thereto methanol (1 ml) solution of sodium metal (50 mg, 2.2 mmol)) was added at room temperature and the mixture was stirred for ten minutes. Acetic acid (100 μl) was added and neutralisation caused, and next, it was diluted with ethyl acetate (150 ml). The obtained reaction mixture liquid was washed with liquid mixture of saturated ammonium chloride aqueous solution (50 ml) and water (50 ml). The organic layer was dried with anhydrous magnesium sulphate, and it was concentrated under reduced pressure. The obtained residue and phosphoric acid (1R, 5R, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2- (diphenylphosphoryl oxy) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (1.26 g, 2.12 mmol)) and diisopropyl ethylamine (0.40 ml, 2.3 mmol)) was dissolved in acetonitrile (20 ml) and the mixture was stirred at room temperature for four hours. The reaction mixture liquid was concentrated under reduced pressure, and it was diluted with dichloromethane, and next, it was washed successively with water and saturated aqueous sodium bicarbonate solution. The dichloromethane solution which was dried on anhydrous magnesium sulphate was concentrated under reduced pressure, and the title compound (1.19 g) was obtained as yellow powder by subjecting the obtained residue to column chromatography (development

solvent : ethyl acetate - dichloromethane - methanol (5:5:1)) using silica gel (30 g) and thereby refined.

(0276)

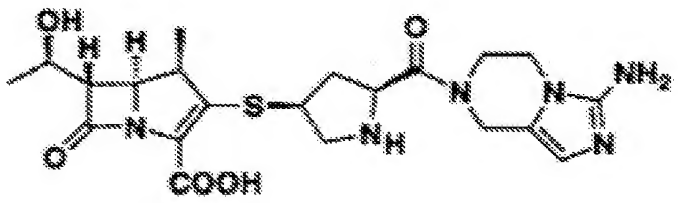
IR spectrum ν_{max} (KBr) cm^{-1}:3368,2968,1772,1712,1665,1591.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.26-1.33 (3H, m), 1.37 (3H, d, J=6.1Hz), 1.90-2.10 (1H, m), 2.65-2.80 (1H, m), 3.28 (1H, brd, J=5.8Hz), 3.30-3.45 (1H, m), 3.47-3.60 (1H, m), 3.62-3.78 (2H, m), 3.80-4.45 (8H, m), 4.60-5.10 (3H, m), 5.15-5.53 (6H, m), 6.49.6.52 (1H, s X2), 7.45-7.66 (6H, m), 8.03-8.24 (6H, m).

Example 31.

(1R, 5S, 6S) -2-((2S, 4S)-2-(3- amino -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio)-6-((R)-1- hydroxyethyl)-1- methyl carbapenem -3- carboxylic acid.

(0277)



(0278)

The title compound (189 mg) was obtained as a colourless cotton-like material from (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-1-(4- nitrobenzyl oxycarbonyl) -2-(3- (4- nitrobenzyl oxycarbonyl) amino -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (1.10 g) using the same procedures as in the Example of the synthesis of (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-2- (5,6,7,8-tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid.

(0279)

IR spectrum ν_{max} (KBr) cm^{-1}:3333,2968,2871,1751,1642,1593.

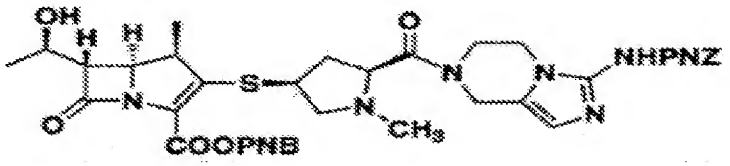
NMR spectrum (270 MHz, D2O) δ ppm:1.19-1.21 (3H, d X2,J=7.3Hz), 1.30 (3H, d, J=6.4Hz), 1.61-1.74 (1H, m), 2.74-2.84 (1H, m), 3.12 (1H, dd, J=12.4, 3.6Hz), 3.21-3.27 (1H, m), 3.36-3.45 (2H, m), 3.80-4.30 (8H, m), 4.65-4.95 (3H, m), 6.64. 6.66 (1H, s X2).

Example 32.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-1- methyl -2-(3- (4- nitrobenzyl oxycarbonyl) amino -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine -4-

ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester.

(0280)



(0281)

Using the same procedures as in the Example of the synthesis of (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-1-(4- nitrobenzyl oxycarbonyl) -2- (5,6,7,8- tetrahydroimidazo (1, 5-a) pyrrolidine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester, the title compound (550 mg) was obtained as a straw-coloured solid from (2S, 4S)-4- acetylthio -1- methyl -2-(3- (4- nitrobenzyl oxycarbonyl) amino -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine (870 mg, 1.73 x 10^{-3}mol).

(0282)

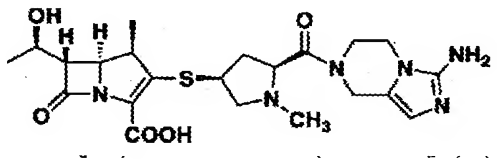
IR spectrum ν_{max} (KBr) cm^{-1}:3402,2969,2933,2855,2790,1768,1709,1638,1590,1521.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.28 (3H, d, J=7.1Hz), 1.38 (3H, d, J=6.3Hz), 1.85-2.00 (1H, m), 2.35 (3H, brs), 2.57-2.85 (2H, m), 3.05-3.35 (3H, m), 3.48-3.60 (1H, m), 3.68-4.03 (4H, m), 4.25-4.95 (5H, m), 5.25 (2H, s), 5.20-5.60 (2H, m), 6.50 (1H, brs), 6.85 (1H, brs), 7.58 (2H, d, J=8.6Hz), 7.68 (2H, d, J=8.7Hz), 8.16-8.27 (4H, m).

Example 33.

(1R, 5S, 6S) -2-((2S, 4S)-2-(3- amino -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl)-1- methylpyrrolidine -4- ylthio)-6-((R)-1- hydroxyethyl)-1- methyl carbapenem -3- carboxylic acid.

(0283)



(0284)

The title compound (143 mg) was obtained as a colourless cotton-like material from (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-1- methyl -2-(3- (4- nitrobenzyl oxycarbonyl) amino -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3-

carboxylic acid 4- nitrobenzyl ester (550 mg, 6.97 X10-4mol) using the same procedures as in the Example of the synthesis of (1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-2- (5,6,7,8-tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid.

(0285)

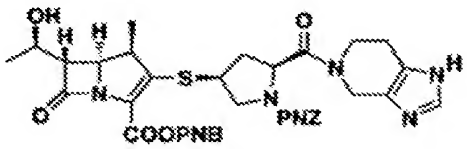
IR spectrum ν_{max} (KBr) cm^{-1}:3333,3144,2967,2869,2789,1755,1652,1595.

NMR spectrum (270 MHz, D2O) δ ppm:1.18,1.20 (3H, d X2,J=7.6Hz), 1.30 (3H, d, J=6.4Hz), 1.61-1.75 (1H, m), 2.34, 2.36 (3H, sX2), 2.80-2.96 (2H, m), 3.14-3.20 (1H, m), 3.32-3.40 (1H, m), 3.40, 3.45 (1H, m), 3.69 (1H, brq, J=8Hz), 3.83-4.10 (5H, m), 4.19 (1H, dd, J=9.1, 2.4Hz), 4.22-4.28 (1H, m), 4.66-4.97 (2H, m), 6.64 (1H, s).

Example 34.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-1-(4- nitrobenzyl oxycarbonyl) -2-(4, 5,6,7- tetrahydroimidazo (4,5- c) pyridine -5- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester.

(0286)



(0287)

Pivaloyl chloride (0.41 ml, 3.3 mmol)) was added at room temperature to dichloromethane (10 ml) suspension of (2S, 4S)-4-(4- methoxybenzyl thio) -1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2-carboxylic acid potassium salt (1.6 g, 3.3 mmol)) and the mixture was stirred for 30 minutes. Thereto 4,5,6,7- tetrahydroimidazo (4,5-c) pyridine (about 800 mg) ((4,5,6,7- tetrahydroimidazo (4,5-c) pyridine dihydrochloride (1.4 g, 7.1 mmol)) was dissolved in methanol (10 ml) solution of metallic sodium (330 mg, 14.4 mmol), and it was neutralized (*?, translator's note : source text unclear*).

(0288)

It was passed through the short column which used alumina (development solvent : ethyl acetate -methanol (1:1)), and precipitated salt was eliminated. Amine was adjusted by concentrating obtained fraction, and was added and the mixture was stirred at room temperature overnight. The reaction liquid was concentrated under reduced pressure, and it was subjected to short column using alumina (development solvent : ethyl acetate -methanol (9:1)) without further treatment. The organic solvent was concentrated down under reduced pressure, and the obtained residue (1.00 g) was dissolved in

trifluoroacetic acid (10 ml) and anisole (2 ml). The mixture was stirred at room temperature for two hours 30 minutes after having added trifluoromethanesulfonic acid (180 µl). The reaction liquid was formed into an azeotrope with 1,2- dichloroethane, and the obtained residue was washed with hexane and ether. This residue and phosphoric acid (1R, 5R, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(diphenylphosphoryl oxy) carbapenem -2- carboxylic acid 4- nitrobenzyl ester (1.19 g, 2.00 mmol)) and diisopropyl ethylamine (0.70 ml, 4.0 mmol)) was dissolved in acetonitrile (10 ml) and were stirred at 0-4°C overnight. The reaction liquid was concentrated, and it was diluted with ethyl acetate and was washed with saturated aqueous sodium bicarbonate solution. The organic layer which was dried on anhydrous magnesium sulphate was concentrated and the obtained residue was subjected to column chromatography (development solvent : dichloromethane - ethyl acetate - methanol (1:1:0)-(5:5:1)) using alumina and thereby refined. The title crude compound (388 mg) was obtained as a straw-coloured solid.

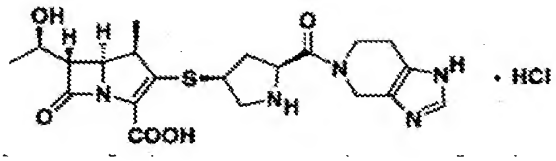
(0289)

IR spectrum ν_{max} (KBr) cm^{-1}:3378,3115,3081,2971,2934,2872,1768,1711,1654,1608.NMR spectrum (270 MHz, CD_3OD) δ ppm:1.15-1.32 (6H, m), 1.75-1.95 (1H, m), 2.45-3.00 (4H, m), 3.35-4.30 (8H, m), 4.40-5.50 (7H, m), 7.05-8.25 (9H, m).

Example 35.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-2- (4,5,6,7- tetrahydroimidazo (4, 5-c) pyridine -5- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid • hydrochloride.

(0290)



(0291)

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-1-(4- nitrobenzyl oxycarbonyl) -2-(4,5,6,7- tetrahydroimidazo (4,5-c) pyridine -5- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3-carboxylic acid 4- nitrobenzyl ester (130 mg, 1.67 X10-4mol)) was dissolved in tetrahydrofuran - water (1:1) mixed solvent (2.5 ml). 10 % Pd-C (200 mg) was added and the mixture was stirred at room temperature under ambient pressure / hydrogen for one hour 30 minutes. The reaction mixture liquid was filtered, and it was diluted with water, and next, it was washed three times with ether. 1.0 N-hydrochloric acid (167 µl, 1.67 x 10^{-4}mol)) was added to the aqueous layer, and the mixture was concentrated under reduced pressure to about 5 ml.

This concentrated liquid was subjected to reverse phase column chromatography (development solvent : water) and thereby refined. Freeze-drying was carried out, and the title compound (20 mg) was obtained as a colourless cotton-like material.

(0292)

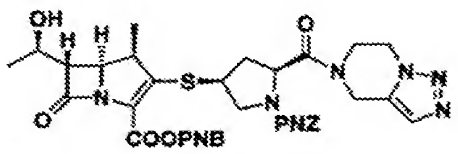
IR spectrum ν_{max} (KBr) cm^{-1}:3405,2970,2931,1752,1650,1598.

NMR spectrum (270 MHz, D2O) δ ppm:1.15-1.23 (3H, m), 1.29, 1.30 (3H, d X2,J=6.4Hz), 1.85-2.10 (1H, m), 2.80-2.95 (2H, m), 3.00-3.17 (2H, m), 3.24-3.38 (1H, m), 3.44-3.55 (2H, m), 3.70-4.30 (6H, m), 4.55-5.00 (2H, m), 7.97, 8.12 (1H, sX2).

Example 36.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-1-(4- nitrobenzyl oxycarbonyl) -2-((1, 2,3) - triazolo (1, 5-a)-5, 6, 7, 8- tetrahydro pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem - 3- carboxylic acid 4- nitrobenzyl ester.

(0293)



(0294)

[a] (2S, 4S)-4- acetylthio -2-((1,2,3) - triazolo (1, 5-a)-5, 6, 7, 8- tetrahydro pyrazine -7- ylcarbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine (1.16 g, 2.44 mmol)) was dissolved in methanol - tetrahydrofuran (3=1, 20 ml) mixed solvent, and methanol (0.6 ml) solution of metallic sodium (57 mg, 2.5 mmol)) was added at -78°C. The reaction temperature was made 0°C and was stirred for 20 minutes. On completion of the reaction, it was diluted with ethyl acetate (about 150 ml), and it was washed respectively with saturated ammonium chloride aqueous solution and saturated aqueous sodium chloride solution, and the organic layer was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation, and mercaptan was obtained.

(0295)

[b] Diphenylphosphoryl chloride (506 μl, 2.44 mmol)) and diisopropyl ethylamine (425 μl, 2.44 mmol)) were added under ice cooling to acetonitrile (20 ml) solution of (1R, 3R, 5R, 6S) -6-((R)-1-hydroxyethyl)-1- methyl -2- oxo carba penam -3- carboxylic acid 4- nitrobenzyl ester (952 mg, 2.44 mmol)) and the mixture was stirred for 30 minutes at the same temperature. Acetonitrile (10 ml) solution of mercaptan obtained in [a] and diisopropyl ethylamine (435 μl, 2.50 mmol)) were added under ice cooling thereto, and the mixture was stirred at the same temperature overnight. On completion

of the reaction, it was diluted with ethyl acetate (about 200 ml) and was washed with water (100 ml), saturated aqueous sodium chloride solution (100 ml). The organic layer was dried with anhydrous magnesium sulphate, and next a straw-coloured solid precipitated when it was concentrated. The precipitate was filtered without further treatment, and it was washed with a little cooled ethyl acetate, and the title compound (1.33 g, 1.69 mmol)) was obtained as straw-coloured powdered form crystals (Mp.111-113°C).

(0296)

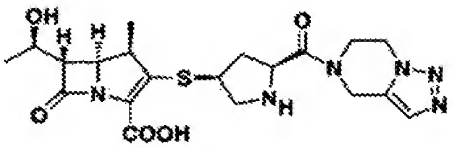
IR spectrum ν_{max} (KBr) cm^{-1}:3450,2971,1773,1709,1671,1607,1522.

NMR spectrum (270 MHz, DMSO-d6) δ ppm:1.15-1.20 (6H, m), 1.65-1.85 (1H, m), 2.80-3.00 (1H, m), 3.15-3.30 (1H, m), 3.63 (1H, m), 3.80-4.50 (8H, m), 4.62-5.46 (8H, m), 7.38, 7.41, 7.44 (1H, s X3), 7.66, 7.64, 7.72 (4H, dX3,J=8.8Hz), 8.03, 8.11, 8.23 (4H, dX3,J=8.8Hz).

Example 37.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-2-((1,2,3) - triazolo (1, 5-a)-5, 6, 7, 8- tetrahydro pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid.

(0297)



(0298)

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-1-(4- nitrobenzyl oxycarbonyl) -2-((1, 2,3) - triazolo (1, 5-a)-5, 6, 7, 8- tetrahydro pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem - 3- carboxylic acid 4- nitrobenzyl ester (100 mg, 1.27 X10-4mol)) was dissolved in water - tetrahydrofuran (1:1) mixed solvent (2 ml). 10 % Pd-C (100 mg) was added and the mixture was stirred at room temperature under ambient pressure / hydrogen for two hours. On completion of the reaction, the catalyst was eliminated by filtration, and the filtrate was diluted with water (about 20 ml). The aqueous layer was washed three times with ether (10 ml), and next, it was concentrated and was refined by chromatography ((development solvent :water-methanol(10:0)-(9:1))) using reverse phase column (20 ml), and freeze-drying was performed, and the target compound (28.5 mg) was obtained as a colourless cotton-like material.

(0299)

IR spectrum ν_{max} (KBr) cm^{-1}:3386,2967,1755,1660,1600.

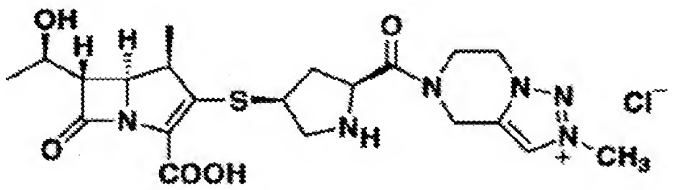
NMR spectrum (270 MHz, D2O) δ ppm:0.98-1.02 (3H, m), 1.09 (3H, d, J=6.5Hz), 1.69-1.86 (1H, m),

2.78-2.94 (1H, m), 3.10-3.22 (1H, m), 3.25-3.28 (1H, m), 3.45-3.53 (1H, m), 3.79-3.89 (2H, m), 4.00-4.14 (3H, m), 4.25-4.44 (2H, m), 4.56-4.70 (1H, m), 4.70-4.86 (2H, m), 7.51, 7.53 (1H, sX2).

Example 38.

7-((2S, 4S)-4-((1R, 5S, 6S) -3- carboxy -6-((R)-1- hydroxyethyl)-1- methyl carbapenem -2- ylthio) pyrrolidine -2- ylcarbonyl)-2- methyl - (1,2,3) - triazolo (1, 5-a)-5, 6, 7, 8- tetrahydro pyrazinium chloride.

(0300)



(0301)

To acetonitrile (15 ml) solution of (1R, 5R, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-1-(4-nitrobenzyl oxycarbonyl) -2-((1,2,3) - triazolo (1, 5-a)-5, 6, 7, 8- tetrahydro pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (1.26 g, 1.60 mmol)), was added trifluoromethanesulfonic acid methyl ester (181 μl, 1.60 mmol)) under ice cooling and the mixture was stirred at the same temperature for 30 minutes. On completion of the reaction, the yellow foam state residue obtained by concentrating under reduced pressure was dissolved in water - tetrahydrofuran (1:1) mixed solvent (20 ml), and 10 % Pd-C (1.2 g) was added. The mixture was stirred at room temperature under ambient pressure / hydrogen for two hours 30 minutes. The reaction liquid was filtered, and it was diluted with water (about 200 ml). The aqueous layer was washed three times with ether (100 ml) and next, it was concentrated to about 20 ml and was passed through column of ion exchange resin (Dowex1-X4 Cl form, 25 ml). The obtained fraction was concentrated to about 20 ml and was refined by column chromatography (development solvent : water) using reverse phase column. The target compound (343 mg) was obtained as a colourless cotton-like material by freeze-drying.

(0302)

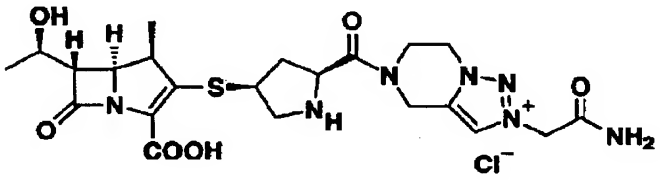
IR spectrum ν_{max} (KBr) cm^{-1}:3392,3111,2967,1757,1665,1599.

NMR spectrum (270 MHz, D2O) δ ppm:1.22 (3H, d, J=7.3Hz), 1.30 (3H, d, J=6.4Hz), 1.98-2.13 (1H, m), 3.03-3.21 (1H, m), 3.30-3.44 (1H, m), 3.46-3.53 (2H, m), 3.74-3.82 (1H, m), 4.05-4.15 (1H, m), 4.17-4.31 (3H, m), 4.36 (3H, s), 4.40-5.20 (7H, m), 8.51 (1H, s).

Example 39.

2- (carbamoylmethyl) -7-((2S, 4S)-4-((1R, 5S, 6S) -3- carboxy -6-((R)-1- hydroxyethyl)-1- methyl carbapenem -2- ylthio) pyrrolidine -2- ylcarbonyl) - (1,2,3) - triazolo (1, 5-a)-5, 6, 7, 8- tetrahydro pyrazinium chloride.

(0303)



(0304)

Iodoacetamide (234 mg, 1.27 x 10^{-3}mol)) was added to acetonitrile (0.5 ml) solution of (1R, 5R, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-((2S, 4S)-1-(4- nitrobenzyl oxycarbonyl) -2-((1,2,3) - triazolo (1, 5-a)-5, 6, 7, 8- tetrahydro pyrazine -7- ylcarbonyl) pyrrolidine -4- ylthio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (100 mg, 1.27 X10-4mol)) and the mixture was stirred at 40-50°C for 48 hours. On completion of the reaction, the solvent was eliminated by distillation, and the residue was washed with ethyl acetate. The obtained residue was dissolved in a mixed solvent of water - tetrahydrofuran (1:1), and 10 % Pd-C (200 mg) was added. The mixture was stirred at room temperature under ambient pressure hydrogen for one hour 30 minutes. The reaction liquid was filtered, and it was diluted with water (about 25 ml). The aqueous layer was washed three times with ether (20 ml) and next, it was concentrated to about 5 ml and was passed through a column of ion exchange resin (Dowex1-X4 Cl form, 3 ml). The obtained fraction was concentrated to about 5 ml and was refined by the column chromatography using a reverse phase column (development solvent : water). Freeze-drying was carried out, and the target compound (22 mg) was obtained as a colourless cotton-like material.

(0305)

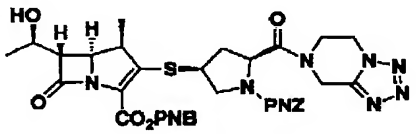
IR spectrum ν_{max} (KBr) cm^{-1}:3401,3182,2974,1753,1698,1665,1607.

NMR spectrum (270 MHz, D2O) δ ppm:1.22 (3H, d, J=7.3Hz), 1.30 (3H, d, J=6.3Hz), 1.95-2.10 (1H, m), 3.00-3.20 (1H, m), 3.33-3.50 (2H, m), 3.67-3.78 (1H, m), 4.00-4.20 (1H, m), 4.21-4.32 (2H, m), 4.45-4.95 (6H, m), 5.06-5.27 (2H, m), 5.61 (2H, s), 8.64 (1H, s).

Example 40.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-1-(4- nitrobenzyl oxycarbonyl) -2-((5,6,7,8- tetrahydro tetrazolo (1, 5-a) pyrazine -7- yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester.

(0306)



(0307)

7-((2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) -2- pyrrolidine carbonyl)-5, 6, 7, 8- tetrahydro tetrazolo (1, 5-a) pyrazine (432 mg, 0.879 mmol)) was dissolved in methanol (2ml)- tetrahydrofuran (1 ml) mixed solvent, and solution of sodium methoxide prepared using metallic sodium (22.4 mg, 0.97 mmol)) and methanol (2 ml) was added under ice cooling. The mixture was stirred under ice cooling for 15 minutes, and next, acetic acid (58.1 mg, 0.97 mmol)) was added, and solution of (2S, 4S)-4- mercapto -1-(4- nitrobenzyl oxycarbonyl) -2-((5,6,7,8- tetrahydro tetrazolo (1, 5-a) pyrazine -7- yl) carbonyl) pyrrolidine was obtained. Meanwhile, (1R, 3R, 5R, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2- oxo carba penam -3- carboxylic acid 4- nitrobenzyl ester (318 mg, 0.88 mmol)) was dissolved in acetonitrile (3 ml), and diisopropyl ethylamine (125 mg, 0.97 mmol)) and diphenyl chlorophosphate (260 mg, 0.97 mmol)) were added under ice cooling and the mixture was stirred for 40 minutes. Next, thereto, diisopropyl ethylamine (125 mg, 0.97 mmol) and solution of the above obtained(2S, 4S)-4- mercapto -1-(4- nitrobenzyl oxycarbonyl) -2-((5,6,7,8- tetrahydro tetrazolo (1, 5-a) pyrazine -7- yl) carbonyl) pyrrolidine was added. Furthermore, the mixture was stirred under ice cooling for two hours, and next, dilute sodium carbonate solution was added, and the mixture was extracted with ethyl acetate. The solvent was eliminated by distillation under reduced pressure, and the residue was subjected to column chromatography using silica gel 18 g, and it was eluted with methanol - chloroform (1:9), and the foamed title compound (337 mg, yield 49 %) was thereby obtained.

(0308)

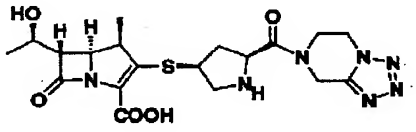
IR spectrum ν_{max} (CHCl3) cm^{-1}:3400,1770,1705,1660,1520,1340.

NMR spectrum [270 MHz, $CDCl_3$-CD_3OD(1:1)] δ ppm:1.28 (3H, d, J=7Hz), 1.33 (3H, d, J=6Hz), 1.9-2.1 (1H, m), 2.6-2.9 (1H, m), 3.0-5.0 (14H, m), 5.1-5.3 (2H, m), 5.27 (1H, d, J=14Hz), 5.49 (1H, d, J=14Hz), 7.4-7.6 (2H, m), 7.67 (2H, d, J=8Hz), 8.24 (4H, d, J=8Hz).

Example 41.

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-2-((5,6,7,8- tetrahydro tetrazolo (1, 5-a) pyrazine -7- yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid.

(0309)



(0310)

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2-(((2S,4S)-1-(4- nitrobenzyl oxycarbonyl) -2-((5, 6, 7, 8- tetrahydro tetrazolo (1, 5-a) pyrazine -7- yl) carbonyl) pyrrolidine -4- yl) thio) carbapenem -3- carboxylic acid 4- nitrobenzyl ester (338 mg, 0.43 mmol)) was dissolved in tetrahydrofuran (3.3 ml) - water (3.3 ml) mixed solvent, and 10 % palladium - carbon catalyst (666 mg) was added and the mixture

was stirred at room temperature under ambient pressure hydrogen for three hours. The catalyst was eliminated by filtration and the filtrate was diluted with water and was washed with ether. The aqueous layer was concentrated under reduced pressure and was submitted to reverse phase column chromatography using Cosmosil C-18PREP (made by Nacalai Tesque) 4.9 g, and the fraction eluted with acetonitrile - water (3:47) was freeze-dried, and the title compound comprising a straw-coloured powder (69 mg, yield 35 %) was thereby obtained.

(0311)

UV spectrum lambda $_{max}$ (H_2O):300nm.

NMR spectrum (270 MHz, D2O) δ ppm:1.23 (3H, d, J=7Hz), 1.30 (3H, d, J=6Hz), 1.9-2.2 (1H, m), 3.0-3.3 (1H, m), 3.38 (1H, dq, J=8, 7Hz), 3.4-3.6 (2H, m), 3.7-3.9 (1H, m), 3.9-4.2 (3H, m), 4.24 (1H, dd, J=8, 2Hz), 4.26 (1H, quintet, J=6Hz), 4.4-5.3 (5H, m).

Reference Example 1.

(2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) -2-(((1S,4S)-5-(4- nitrobenzyl oxycarbonyl) -2 ,5-diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine.

(2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) -2- pyrrolidine carboxylic acid potassium salt (1.00 g, 2.46 mmol)) was suspended in dichloromethane (10 ml), and pivaloyl chloride (288 μl, 2.34 mmol)) was added under ice cooling and the mixture was stirred at room temperature for 30 minutes. Next, triethylamine (512 μl, 3.68 mmol)) was added, and next, dichloromethane (8 ml) solution of (1S, 4S)-2-(4- nitrobenzyl oxycarbonyl) -2 ,5- diazabicyclo (2.2.1) heptane (739 mg, 2.66 mmol)) was added under ice cooling. The mixture was stirred for 30 minutes, and next, it was diluted with dichloromethane, and it was washed with water and saturated aqueous sodium chloride solution. The solvent was eliminated by distillation under reduced pressure and was submitted to column chromatography using silica gel (100 ml), and it was eluted with a mixed solvent of ethyl acetate - dichloromethane - methanol (7:3:1), and the pale yellow foamed title compound (1.18 g, yield 77 %) was thereby obtained.

(0312)

IR spectrum ν_{max} (liq)cm^{-1}:1706,1656,1522,1346,1109.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.80-2.13 (3H, m), 2.34 and 2.35 (3H, sX2), 3.33-3.57 (4H, m), 3.77-4.17 (3H, m), 4.23-5.73 (3H, m), 5.15-5.30 (4H, m), 7.42-7.58 (4H, m), 8.22 (4H, d, J=9Hz).

Reference Example 2.

(2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) -2-(((1S,4S)-5- methyl -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine

[2S, 4S]-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) -2- pyrrolidine carboxylic acid potassium salt

(800 mg, 1.97 mmol)) was suspended in dichloromethane (8 ml) and pivaloyl chloride (230 μl, 1.87 mmol)) was added under ice cooling and the mixture was stirred at room temperature for one hour. Next, triethylamine (412 μl, 2.95 mmol)) was added, and next, dichloromethane solution (3 ml) of (1S, 4S)-2- methyl -2 ,5- diazabicyclo (2.2.1) heptane (287 mg, 2.56 mmol)) was added under ice cooling. The mixture was stirred for two hours 40 minutes, and it was washed sequentially with water, saturated aqueous sodium chloride solution and thereafter saturated aqueous sodium hydrogen carbonate. The residue obtained by eliminating the solvent by distillation under reduced pressure, and was subjected to chromatography of Lobar column (type B), and it was eluted with a mixed solvent of dichloromethane - ethyl acetate - methanol (7:3:1), and pale yellow foamed title compound (559 mg, yield 65 %) was thereby obtained.

(0313)

IR spectrum ν_{max} (KBr) cm^{-1}:1710,1655,1522,1440,1345,1168,1112.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.67-2.1 (3H, m), 2.34 (3H, s), 2.43 (3H, s), 2.60-2.85 (2H, m), 3.05-3.67 (5H, m), 3.90-4.80 (4H, m), 5.04 and 5.34 (2H X1/2,ABq, J=14Hz), 5.20 and 5.22 (2H X1/2,ABq, J=13Hz), 7.42-7.56 (2H, m), 8.22 (2H, d, J=8Hz).

Mass spectrum m/z:463 (M^++1), 419,381,247,203,165,136,111,81 (100 %), 68.

Reference Example 3

(2S, 4S)-4-(4- methoxybenzyl thio) -1- methyl -2-(((1S,4S)-5-(4- nitrobenzyl oxycarbonyl) -2 ,5- diazabicyclo (2.2.1) heptane -2- yl) carbonyl) pyrrolidine.

(2S, 4S)-1- methyl -4-(4- methoxybenzyl thio) pyrrolidine -2- carboxylic acid (1.00 g, 3.55 mmol)) was suspended in acetonitrile (10 ml), and 1,1 '- carbonyldiimidazole (634 mg, 3.91 mmol)) was added at room temperature and next, the mixture was stirred at 35°C for two hours.

Next, acetonitrile (15 ml) solution of (1S, 4S)-2-(4- nitrobenzyl oxycarbonyl) -2 ,5- diazabicyclo (2.2.1) heptane (1.09 g, 3.91 mmol)) was added under ice cooling. The mixture was stirred at room temperature for three hours, and next, it was concentrated, and dichloromethane was added to the residue and the mixture was washed with water, and furthermore it was washed with saturated aqueous sodium chloride solution. The oily substance obtained by eliminating the solvent by distillation under reduced pressure, was subjected to column chromatography using 80 ml silica gel, and it was eluted with a mixed solvent of methanol - dichloromethane (1:15), and pale brown foamed title compound (1.66 g, yield 87 %) was thereby obtained.

(0314)

IR spectrum ν_{max} (KBr) cm^{-1}:1708,1641,1512,1432,1405,1346,1247,1176,1102.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.67-2.02 (4H, m), 2.25 (3H x 1/3,s), 2.30 (3H x 2/3,s), 2.37-2.63 (2H, m), 2.90-3.20 (3H, m), 3.34-3.66 (4H, m), 3.70 (2H, s), 3.79 (3H, s), 4.54-4.70 (1H, m), 5.24

(2H x 1/2,s), 5.15 and 5.26 (2H X1/2,ABq, J=14Hz), 6.82-6.88 (2H, m), 7.18-7.26 (2H, m), 7.53 (2H, d, J=8Hz), 8.22 (2H, d, J=8Hz).
Mass spectrum m/z:540(M^+), 417,388,321,261,236 (100 %), 136,121,82.

Reference Example 4

7- benzyl -2 ,4- dioxo -3- methyl -1 ,4- diazabicyclo (3.3.0) octane.

To a solution of N- (Methoxymethyl) -N- (trimethylsilylmethyl) benzylamine (5.75 g, 24.2 mmol)) in dichloromethane (50 ml), was added N- methyl maleimide (2.24 g, 20.2 mmol)), and thereafter trifluoroacetic acid (230 mg, 2.02 mmol)) was added under ice cooling. The reaction liquid was returned to room temperature and was stirred for one hour, and next, ice cooled dilute sodium carbonate solution was added, and it was washed. The solvent was eliminated by distillation under reduced pressure and the obtained crystalline residue was recrystallised from acetone : hexane (1:2) mixed solvent , and the title compound which had melting point 91-92°C (3.93 g, yield 80 %) was thereby obtained.

(0315)

Elemental analysis.
Theoretical value C:68.83,H:6.60,N:11.47
Analysis value C:69.09,H:6.77,N:11.59
IR spectrum ν_{max} (CHCl3) cm^{-1}:2800,1700,1438.
NMR spectrum (270 MHz, $CDCl_3$) δ ppm:2.40 (2H, br.s), 3.02 (3H, s), 3.20 (2H, br.s), 3.28 (2H, br.s), 3.60 (2H, br.s), 7.2-7.3 (5H, m).
Mass spectrum m/z:244(M^+), 167,153,132,118,91 (100 %).

Reference Example 5

3- benzyl -7- methyl -1 ,4- diazabicyclo (3.3.0) octane.

7- benzyl -2 ,4- dioxo -3- methyl -1 ,4- diazabicyclo (3.3.0) octane (4.58 g, 18.8 mmol)) was dissolved in benzene (39 ml) and 3.4M-Red-Al toluene solution (made by Aldrich company) (21.4 ml, 72.8 mmol)) was added under ice cooling and, under nitrogen gas atmosphere, the mixture was heated under reflux for three hours. The reaction liquid was cooled with ice, and 10 % sodium hydroxide aqueous solution (29.1 ml) was added, and it was returned with ice cooling to room temperature over five minutes, and it was stirred for 15 minutes, and it was extracted with benzene, and it was washed with saturated aqueous sodium chloride solution. The solvent was eliminated by distillation, and the title compound (4.04 g, yield 99.6 %) was thereby obtained.

(0316)

IR spectrum ν_{max} (CHCl3) cm^{-1}:2950,2905,2795,1473,1450,1140,890,695.
NMR spectrum (270 MHz, $CDCl_3$) δ ppm:2.2-2.4 (4H, m), 2.35 (3H, s), 2.5-2.6 (2H, m), 2.6-2.8 (4H,

m), 3.60 (2H, s), 7.2-7.4 (5H, m).
Mass spectrum m/z:216(M^+), 201,125 (100 %), 91.

Reference Example 6.

3- methyl -3 ,7- diazabicyclo (3.3.0) octane • diformate.

Formic acid (1.2 ml, 31.8 mmol)) and palladium black (500 mg) were added to a solution comprising 3-benzyl -7- methyl -1 ,4- diazabicyclo (3.3.0) octane (2 g, 9 mmol)) dissolved in methanol (23 ml), and the mixture was heated at a bath temperature of 60°C for three hours.

(0317)

The catalyst was eliminated by filtration, and the solvent was eliminated by distillation under reduced pressure, and the title compound (2.0 g, yield 99 %) was obtained as an oily substance.

(0318)

IR spectrum ν_{max} (CHCl3) cm^{-1}:2950,2800,1663,1620,1590.
NMR spectrum (60 MHz, $CDCl_3$) δ ppm:2.43 (3H, s), 2.5-3.8 (10H, m), 8.48 (2H, s), 10.63 (3H, s).
Mass spectrum m/z:126, 96 (100 %), 82.

Reference Example 7.

(2S, 4S)-4- acetylthio -2-((7- methyl -3 ,7- diazabicyclo (3.3.0) octane -3- yl] carbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine.

(2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2- carboxylic acid potassium salt (3.034 g, 7.46 mol) was suspended in dichloromethane (60 ml), and pivaloyl chloride (900 mg, 7.46 mol) was added under ice cooling and the mixture was stirred at room temperature for 30 minutes. This solution was added under ice cooling dropwise to a solution of 3- methyl -3 ,7- diazabicyclo (3.3.0) octane • diformate (1.95 g, 8.93 mol) and diisopropyl ethylamine (2.31 g, 17.9 mol) dissolved in dichloromethane (22 ml). The liquid mixture was stirred at room temperature for two hours, and next, it was diluted with ethyl acetate, and it was washed with dilute sodium carbonate solution, and next it was washed with saturated aqueous sodium chloride solution. The solvent was eliminated by distillation under reduced pressure, and the residue was subjected to column chromatography using silica gel 40 g, and it was eluted with methanol - ethyl acetate (6:94-50:50), and the title compound (3.0 g, yield 84.3 %) was thereby obtained.

(0319)

IR spectrum ν_{max} (CHCl3) cm^{-1}:2960,1695,1690,1645,1440,1428,1345,1120.
NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.9-2.0 (2H, m), 2.32 (3H, s), 2.34 (3H, s), 2.4-2.6 (2H, m), 2.6-3.1 (2H, m), 3.2-3.6 (2H, m), 3.6-3.8 (2H, m), 3.9-4.0 (2H, m), 4.1-4.2 (2H, m), 4.5-4.6 (2H, m),

5.07 (1H x 1/4,d, J=15Hz), 5.09 (1H x 1/4,d, J=15Hz), 5.23 (2H x 1/2,s), 5.32 (1H x 1/4,d, J=15Hz), 5.34 (1H x 1/4,d, J=15Hz), 7.4-7.5 (2H x 1/2,m), 7.50 (2H x 1/2,d, J=9Hz), 8.22 (2H, d, J=9Hz).

Reference Example 8.

(2S, 4S)-4- mercapto -2-((7- methyl -3 ,7- diazabicyclo (3.3.0) octane -3- yl] carbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine.

(2S, 4S)-4- acetylthio -2-((7- methyl -3 ,7- diazabicyclo (3.3.0) octane -3- yl] carbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine (2.95 g, 6.19 mmol)) was dissolved in methanol (29 ml), and sodium methoxide solution prepared using metallic sodium (144 mg, 6.26 mmol)) and methanol (5 ml) was added under ice cooling. The mixture was stirred under ice cooling for 15 minutes, and next, acetic acid (377 mg, 6.28 mmol)) was added. Ethyl acetate was added to the reaction liquid, and it was diluted and was washed with ice cooled saturated aqueous sodium chloride solution.

The crystalline residue obtained by eliminating the solvent by distillation under reduced pressure, was washed with benzene, and the straw-coloured title compound (1.4 g, yield 52 %) was obtained as crystals.

(0320)

Melting point 157-160°C.

(0321)

Elemental analysis.

Theoretical value C:55.28,H:6.03,N:12.89,S:7.38

Analysis value C:55.22,H:6.12,N:12.61,S:7.04

IR spectrum ν_{max} (CHCl3) cm^{-1}:2980,2940,2780,1700,1642,1520,1430,1400,1342.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.9-2.0 (2H, m), 2.28 (3H x 1/4,s), 2.34 (3H x 1/4,s), 2.40 (3H x 1/2,s), 2.4-3.0 (6H, m), 3.0-3.7 (5H, m), 3.7-3.9 (1H, m), 3.9-4.2 (2H, m), 4.4-4.6 (1H, m), 5.0-5.4 (1H, m), 5.20 (1H, s), 7.49 (1H, d, J=9Hz), 7.50 (1H, d, J=9Hz), 8.22 (1H, d, J=9Hz), 8.23 (1H, d, J=9Hz).

Mass spectrum m/z:434(M^+), 417,401,383,357,314,298,281,254,237,203, 191,153,136,125 (100 %), 96,82,78.

Reference Example 9.

3,7- dibenzyl -2 ,4- dioxo -3 ,7- diazabicyclo (3.3.0) octane.

N- benzyl maleimide (4.28 g, 22.9 mmol)) was added to a solution comprising N- methoxymethyl -N- (trimethylsilylmethyl) benzylamine (6.51 g, 27.4 mmol)) dissolved in methylene chloride (60 ml), and 1M trifluoroacetic acid - methylene chloride solution (2.29 ml) was added under ice cooling. The reaction liquid was returned to room temperature and was stirred for one hour, and next, dilute sodium carbonate solution was added, and it was washed. Drying (Magnesium sulphate) was carried out on the

organic layer, and the crystalline residue obtained by concentrating down the solvent under reduced pressure was washed with ether, and the title compound (7.09 g, 97 %) was thereby obtained.

(0322)

Melting point :101-101.5°C.

(0323)

IR spectrum ν_{max} (KBr) cm^{-1}:2814,1699,1401,1347..

NMR spectrum (60 MHz, $CDCl_3$) δ ppm:2.15-2.65 (2H, m), 3.05-3.50 (4H, m), 3.63 (2H, s), 4.68 (2H, s), 6.90-7.65 (10H, m).

Mass spectrum m/z:320 (M^+, 100 %), 243,229,201,181,158,151,132,118,91.

Reference Example 10

3,7- dibenzyl -3 ,7- diazabicyclo (3.3.0) octane.

3,7- dibenzyl -2 ,4- dioxo -3 ,7- diazabicyclo (3.3.0) octane (5.3 g, 16.54 mmol)) was dissolved in benzene (50 ml) and under a nitrogen atmosphere 3.4M-Red-Al toluene solution (made by Aldrich Co.) (16.93 ml, 57.52 mmol)) was added and the mixture was heated under reflux for two hours. The reaction liquid was cooled with ice, and 10 % sodium hydroxide aqueous solution (29.7 ml, 72.50 mmol)) was added, and the mixture was returned to room temperature and was stirred for 20 minutes, and it was extracted with benzene, and the benzene layer was washed with saturated aqueous sodium chloride solution. The organic layer was dried with magnesium sulphate, and the solvent was eliminated under reduced pressure by distillation, and the residue was subjected to column chromatography using silica gel (50 g), and it was eluted with the ethyl acetate solvent, and the title compound (4.33 g, 89 %) was thereby obtained as an oily substance.

(0324)

IR spectrum ν_{max} (CHCl3) cm^{-1}:2950,2900,2795,1495,1455,1145,910.

NMR spectrum (60 MHz, $CDCl_3$) δ ppm:1.90-3.10 (10H, m), 3.57 (4H, s), 6.95-7.60 (10H, m).

Mass spectrum m/z:292(M^+), 201,172,158,134,120,91 (100 %).

Reference Example 11

3,7- diazabicyclo (3.3.0) octane • dihydrochloride.

3,7- dibenzyl -3 ,7- diazabicyclo (3.3.0) octane (2.6 g, 8.89 mmol)) was dissolved in 5 % formic acid - methanol (40 ml), and palladium black (720 mg) was added, and the mixture was heated at bath temperature 60°C for four hours. The catalyst was eliminated by filtration, and the filtrate was concentrated under reduced pressure and the obtained residue was dissolved in methanol (17 ml), and 4N hydrochloric acid - dioxane (6.5 ml) was added under ice cooling and the mixture was stirred at room temperature for one hour. The reaction liquid was concentrated under reduced pressure, and the

title compound (1.38 g, 90 %) was thereby obtained as a solid.

(0325)

IR spectrum ν_{max} (KBr) cm^{-1}:3270,2935,2761,1648,1590,1535,1465,1381.

NMR spectrum (270 MHz, CD_3OD) δ ppm:3.29-3.41 (6H, m), 3.42-3.62 (4H, m).

Reference Example 12

3- (tert butoxycarbonyl) -3 ,7- diazabicyclo (3.3.0) octane.

3,7- diazabicyclo (3.3.0) octane • dihydrochloride (1.13 g, 6.1 mmol)) was dissolved in methanol (20 ml) and triethylamine (617 mg, 6.1 mmol)) was added under ice cooling and the mixture was stirred for ten minutes. Di (tertbutyl) di carbonate (1.33 g, 6.1 mmol) dissolved in tetrahydrofuran (20 ml) was added and the mixture was stirred for 30 minutes. Thereafter triethylamine (617 mg, 6.1mmol)) was added, and the reaction liquid was concentrated under reduced pressure after stirring for 15 minutes, and the residue was subjected to column chromatography using silica gel (15 g), and it was eluted with 50 % methanol - ethyl acetate -2 % triethylamine, and the title compound (801 mg, 62 %) was obtained as a solid.

(0326)

IR spectrum ν_{max} (CHCl3) cm^{-1}:1680,1490,1410,1385,1170,875.

NMR spectrum (60 MHz, $CDCl_3$) δ ppm:1.44 (9H, s), 2.10-2.95 (6H, m), 3.05-3.80 (5H, m).

Mass spectrum m/z:212(M^+), 155,139,111,95,82,68,57 (100 %).

Reference Example 13

3- (tert butoxycarbonyl) -7- (N-(4- nitrobenzyl oxycarbonyl) aceto imidoyl)-3 ,7- diazabicyclo (3.3.0) octane

3- (tert butoxycarbonyl) -3 ,7- diazabicyclo (3.3.0) octane (560 mg, 2.64 mmol)) was dissolved in dried acetonitrile (15 ml) and 4N hydrochloric acid - dioxane (0.66 ml, 2.64 mmol)) was added under ice cooling and the mixture was stirred for 15 minutes. Thereafter N- (4- nitrobenzyl oxycarbonyl) acetamide (720 mg, 3.03 mmol)) was added and the mixture was stirred at bath temperature 50°C for two hours. The precipitated insolubles were eliminated by filtration, and the filtrate was concentrated under reduced pressure, and the obtained residue was subjected to column chromatography using silica gel (15 g), and it was eluted with 10-20 % acetone - ethyl acetate mixed solvent, and a white foamed title compound (580 mg, 51 %) was thereby obtained.

(0327)

IR spectrum ν_{max} (CHCl3) cm^{-1}:1685,1675,1550,1520,1405,1345,1245,1160,1070.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.46 (9H, s), 2.33 (3H, s), 2.93-3.02 (2H, m), 3.28-3.40 (2H,

m), 3.41 (1H, dd, J=4.4, 11.2Hz), 3.47-3.66 (2H, m), 3.63 (1H, dd, J=7.3, 11.2Hz), 3.73-3.84 (2H, m), 5.23 (2H, s), 7.57 (2H, d, J=8.8Hz), 8.20 (2H, d, J=8.8Hz).

Reference Example 14.

(((2S,4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2- yl) carbonyl)-7- (N-(4- nitrobenzyl oxycarbonyl) aceto imidoyl)-3 ,7- diazabicyclo (3.3.0) octane.

3- (tert butoxycarbonyl) -7- (N-(4- nitrobenzyl oxycarbonyl) aceto imidoyl)-3 ,7- diazabicyclo (3.3.0) octane (730 mg, 1.69 mmol)) was dissolved in dried acetonitrile (12 ml) and under a nitrogen atmosphere 4N hydrochloric acid - dioxane solution (2.52 ml, 10.14 mmol)) was added at 0°C and the mixture was stirred for 20 minutes, and thereafter was returned to room temperature and was stirred for a further one hour. The reaction liquid was concentrated under reduced pressure, and 7- (N-(4- nitrobenzyl oxycarbonyl) aceto imidoyl)-3 ,7- diazabicyclo (3.3.0) octane • hydrochloride (685 mg, 1.69 mmol)) was obtained. Meanwhile, (2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2- carboxylic acid potassium salt (687 mg, 1.69 mmol)) was suspended in dried methylene chloride (15 ml), and pivaloyl chloride (194 mg, 1.61 mmol)) was added under ice cooling and the mixture was returned to room temperature and was stirred for one hour. A solution comprising the above obtained 7- (N-(4- nitrobenzyl oxycarbonyl) aceto imidoyl)-3 ,7- diazabicyclo (3.3.0) octane • hydrochloride dissolved in dried dimethylacetamide (4 ml) was added to this reaction liquid, and thereafter diisopropyl ethylamine (655 mg, 5.07 mmol)) was added. The reaction liquid was returned to room temperature and was stirred for one hour, and next, it was diluted with ethyl acetate, and it was washed with dilute sodium carbonate solution and saturated aqueous sodium chloride solution. The organic layer was dried with magnesium sulphate, and the solvent was concentrated under reduced pressure, and the obtained residue was subjected to column chromatography using silica gel (20 g), and it was eluted with a mixed solvent of methanol -50 % ethyl acetate • methylene chloride (4:96-6:94), and the pale yellow foamed title compound (950 mg, 82 %) was thereby obtained.

(0328)

IR spectrum ν_{max} (CHCl3) cm^{-1}:1690,1655,1520,1425,1325,1240,1160.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm :1.89-2.17 (2H, m), 2.34 (3H, s), 2.34 (3H, s), 2.56-2.71 (1H, m), 2.99-3.12 (2H, m), 3.31-3.60 (4H, m), 3.63-4.22 (8H, m), 4.42-4.52 (1H, m), 5.15-5.26 (4H, m), 7.43-7.51 (2H, m), 7.56-7.64 (2H, m), 8.19 (2H, d, J :3.4 Hz), 8.22 (2H, d, J :3.4 Hz).

Reference Example 15

2-(N- (t- butoxycarbonyl) -N-((3- pyrazolyl) methyl) amino) ethanol.

3- (chloromethyl) pyrazole hydrochloride (170 mg, 1.11 mmol) prepared using the method of R.G.Jones (J.Am.Chem.Soc.71,3994(1949)), and 2- aminoethanol (405 mg, 6.63 mmol) was dissolved in acetonitrile (1.7 ml) - ethanol (0.5 ml) mixed solvent and the mixture was stirred at 60-70°C for one

hour 42 minutes. The mixture was under reduced pressure heated to 90°C, and the solvent and most of the 2- aminoethanol were eliminated by distillation. Methanol (2 ml) and acetonitrile (2 ml) were added to the residue and dissolution caused, and di (tert butyl) dicarbonate (740 mg, 3.39 mmol)) and triethylamine (336 mg, 3.32 mmol)) were added and the mixture was stirred at 50°C for one hour 30 minutes. The solvent was eliminated by distillation under reduced pressure, and the residue was dissolved in ethyl acetate and was washed with dilute sodium carbonate solution and saturated aqueous sodium chloride solution. The solvent was eliminated by distillation under reduced pressure, and the residue was subjected to column chromatography using silica gel (8 g), and it was eluted with ethyl acetate, and the oily title compound (169 mg, yield 63 %) was thereby obtained.

(0329)

IR spectrum ν_{max} (CHCl3) cm^{-1}:3460,3230,2970,1680,1460,1405,1365,1240,1160,1040.
NMR spectrum (60 MHz, $CDCl_3$) δ ppm:1.40 (9H, s), 3.43 (2H, t, J=5Hz), 3.70 (2H, t, J=5Hz), 4.44 (2H, s), 6-9 (2H, br), 6.15 (1H, d, J=2Hz), 7.43 (1H, d, J=2Hz).
Mass spectrum m/z:241(M^+), 211,199,185,168,155,140,123,110,81 (100 %), 57.

Reference Example 16.

5- (tert butoxycarbonyl) -4, 5, 6, 7- tetrahydropyrazolo (2,3- a) pyrazine).

Triphenylphosphine (120 mg, 0.46 mmol)) was added a little at a time to a mixture of 2-(N- (tert butoxycarbonyl) -N-((3- pyrazolyl) methyl) amino) ethanol (50 mg, 0.21 mmol)), carbon tetrachloride (0.5 ml) and pyridine (0.5 ml), and during this addition, the mixture was stirred at 50°C. The addition took two hours 30 minutes . After cooling, mixture was diluted with ethyl acetate and was washed with dilute sodium carbonate solution and saturated aqueous sodium chloride solution. The solvent was eliminated by distillation under reduced pressure, and N,N- dimethylformamide (6 ml), diisopropyl ethylamine (70 mg, 0.54 mmol)) and sodium iodide (50 mg, 0.33 mmol)) were added to the residue, and the mixture was stirred at 110°C for one hour. After cooling, the mixture was diluted with ethyl acetate and was washed with dilute sodium carbonate solution and saturated aqueous sodium chloride solution. The solvent was eliminated by distillation under reduced pressure, and the residue was subjected to separating and recovering thin layer chromatography, and it was developed with ethyl acetate - hexane (2:3), and colourless oily title compound (13 mg, yield 30 %) was thereby obtained.

(0330)

IR spectrum ν_{max} (CHCl3) cm^{-1}:2980,1685,1410,1368,1240,1164,1138.
NMR spectrum (60 MHz, $CDCl_3$) δ ppm:1.48 (9H, s), 3.83 (2H, dd, J=8,6Hz), 4.16 (2H, dd, J=8,6Hz), 4.64 (2H, brs), 6.0-6.2 (1H, m), 7.50 (1H, d, J=2Hz).
Mass spectrum m/z:223(M^+), 166 (100 %), 150,122,57.

Reference Example 17.

4,5,6,7- tetrahydropyrazolo (2,3- a) pyrazine • dihydrochloride)

Hydrochloric acid (4N- dioxane solution, 8 ml, 32 mmol)) was added under ice cooling to ethyl acetate (0.3 ml) solution of 5- (tert-butoxycarbonyl) -4, 5, 6, 7- tetrahydropyrazolo (2,3-a) pyrazine (400 mg, 1.79 mmol). The mixture was stirred at room temperature for one hour, and next, the solvent and excess hydrochloric acid were eliminated by distillation under reduced pressure, and ethyl acetate was added to the residue, and the insoluble precipitate was recovered by filtration, and the title compound which had melting point 120°C (decomposition) (354 mg, yield 100 %) was thereby obtained as a colourless powder.

(0331)

NMR spectrum (270 MHz, CD_3OD) δ ppm:3.81 (2H, t, J=6Hz), 4.47 (2H, t, J=6Hz), 4.57 (2H, brs), 6.35-6.40 (1H, m), 7.66 (1H, d, J=2Hz).

Reference Example 18.

(2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) -2-((4,5,6,7- tetrahydropyrazolo (2,3- a) pyrazine -5- yl) carbonyl) pyrrolidine.

(2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2- carboxylic acid potassium salt (1050 mg, 2.58 mmol) was suspended in dichloromethane (9 ml), and pivaloyl chloride (310 mg, 2.58 mmol) was added under ice cooling and the mixture was stirred at room temperature for 30 minutes. Thereafter a mixture of 4,5,6,7- tetrahydropyrazolo (2,3-a) pyrazine dihydrochloride (461 mg, 2.35 mmol), triethylamine (792 mg, 7.83 mmol) and N,N- dimethylformamide (20 ml) was added thereto under ice cooling. The mixture was stirred at room temperature for two hours, and next, it was diluted with ethyl acetate, and it was washed with water and saturated aqueous sodium chloride solution. The solvent was eliminated by distillation under reduced pressure, and the residue was subjected to column chromatography using silica gel (15 g), and it was eluted with ethyl acetate, and the pale yellow foamed title compound (1034 mg, yield 93 %) was thereby obtained.

(0332)

IR spectrum ν_{max} (CHCl3) cm^{-1}:3000,1700,1660,1520,1340,1120.

NMR spectrum (60 MHz, $CDCl_3$) δ ppm:1.8-2.5 (1H, m), 2.30 (3H, s), 2.5-3.0 (1H, m), 3.5-5.5 (8H, m), 4.85 (2H, s), 5.22 (2H, s), 6.11 (1H, br.s), 7.2-7.7 (3H, m), 8.28 (2H, d, J=9Hz).

Reference Example 19

4- (chloromethyl) imidazole • hydrochloride.

Thionyl chloride (10 ml) was mixed slowly with 4- (hydroxymethyl) imidazole hydrochloride (5.0 g, 4.2 X10-2mol)) and the mixture was heated under reflux on a steam bath for 20 minutes. On completion

of the reaction, the mixture was allowed to cool, and excess thionyl chloride was eliminated by distillation. The obtained straw-coloured crude crystals was dissolved in iced water, and it was washed with ether. The aqueous layer was concentrated, and the target compound (6.1 g) was obtained as a colourless crude crystals.

(0333)

NMR spectrum (270 MHz, CD_3OD) δ ppm:4.82 (2H, s), 7.65 (1H, s), 8.96 (1H, s).

Reference Example 20

7- benzyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine.

4- (chloromethyl) imidazole hydrochloride (6.0 g, 3.9 x 10^{-2}mol)) was dissolved in methanol - acetonitrile (1:1) mixed solvent (30 ml), and thereto N- benzyl ethanolamine (6.8 g, 4.5 X10-2mol)) was added at room temperature. At room temperature, triethylamine (14 ml) was added slowly while stirring reaction mixture liquid. The reaction solution was concentrated after one hour, and toluene (20 ml) was added and the solution was concentrated and dried again. Thionyl chloride (15 ml) was slowly added to the obtained residue at room temperature and the mixture was heated under reflux on a steam bath for 15 minutes. The excess thionyl chloride was eliminated by distillation, and dissolution in water (100 ml) caused. The aqueous layer was washed twice with ether (100 ml) and was concentrated and dried. Acetonitrile (180 ml) was added to obtained residue, and triethylamine (20 ml) was slowly added at room temperature while stirring, and next, the reaction mixture liquid was refluxed for three hours. On completion of the reaction, the reaction liquid was concentrated, and it was diluted with ethyl acetate, and it was washed with 2N sodium hydroxide aqueous solution and saturated aqueous sodium chloride solution. The organic layer was dried with anhydrous magnesium sulphate, and next it was concentrated, and the residue was refined with silica gel column chromatography (development solvent :ethyl acetate - methanol (10:0) -(9:1)), and the title compound (2.3 g) was obtained as yellow crystals (Mp. 81-83°C).

(0334)

IR spectrum ν_{max} (CHCl3) cm^{-1}:2950,2800,2750,1650.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:2.84 (2H, t, J=5.3Hz), 3.66 (2H, s), 3.70 (2H, s), 4.03 (2H, t, J=5.3Hz), 6.73 (1H, s), 7.27-7.36 (5H, m), 7.39 (1H, s).

Reference Example 21

5,6,7,8- tetrahydroimidazo (1, 5-a) pyrazine • dihydrochloride.

Palladium black (200 mg) and formic acid 0.5 ml were added to methanol (20 ml) solution of 7- benzyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine (1.77 g, 8.30 mmol) and the mixture was stirred at about 70°C for five hours. On completion of the reaction, water (about 10 ml) was added, and filtration carried out. The filtrate was concentrated, and the residue was dissolved in 1N-HCl aqueous solution and the solution was stirred at about 90°C for two hours. The reaction mixture liquid was concentrated without

further treatment, and methanol was added, and the mixture was left to stand. The precipitated crystals were recovered by filtration, and the title compound (1.39 g) was obtained as colourless acicular crystals (Mp245-249°C).

(0335)

IR spectrum ν_{max} (KBr) cm^{-1}:3422,3097,3066,3001,2914,2788,2721,2606,2571,2504,1610,1587.
NMR spectrum (270 MHz, D2O) δ ppm:3.84 (2H, t, J=5.9Hz), 4.64 (2H, s), 4.65 (2H, t, J=5.9Hz), 7.51 (1H, s), 8.87 (1H, s).

Reference Example 22

(2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) -2- (5,6,7,8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine.

Pivaloyl chloride (0.61 ml, 5.0 X10-3mol)) was added to dichloromethane (40 ml) suspension of (2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2- carboxylic acid potassium salt (2.0 g, 5.0 X10-3mol)) at room temperature and the mixture was stirred for 30 minutes. Triethylamine (1.5 ml, 1.1 x 10^{-2}mol)) and 5,6,7,8- tetrahydroimidazo (1, 5-a) pyrazine dihydrochloride (1.0 g, 5.1 X10-3mol)) were added thereto at room temperature and the mixture was stirred for 30 minutes. The reaction liquid was concentrated and was dissolved in ethyl acetate, and next, it was washed with water, saturated sodium hydrogen carbonate and saturated aqueous sodium chloride solution, and the organic layer was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation, and next, the residue was subjected to column chromatography (development solvent :ethyl acetate - methanol(7:3)) using alumina, and the title compound (1.59 g) was obtained as a straw-coloured foamed substance.

(0336)

IR spectrum ν_{max} (CHCl3) cm^{-1}:2955,1695,1660,1605.
NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.85-2.05 (1H, m), 2.34 (3H, s), 2.70-2.90 (1H, m), 3.43-3.52 (1H, m), 3.80-3.95 (1H, m), 3.95-4.35 (5H, m), 4.58-5.05 (3H, m), 5.17-5.30 (2H, m), 6.89, 6.93 (1H, s X2), 7.35, 7.50 (2H, dX2,J=8.4Hz), 7.47, 7.60, 7.74 (1H, sX3), 8.07, 8.13, 8.22 (2H, dX3,J=8.4Hz).

Reference Example 23

4- (chloromethyl) -5- methyl imidazole • hydrochloride.

Thionyl chloride (8.0 ml) was slowly mixed with 4- (hydroxymethyl) -5- methyl imidazole • hydrochloride (6.6 g, 4.4 x 10^{-2}mol)) and the mixture was heated under reflux on a steam bath for ten minutes. On completion of the reaction, the mixture was allowed to cool, and the excess thionyl chloride was eliminated by distillation. The obtained solid was washed with ether and ethyl acetate, and the title compound (7.3 g) was obtained as a white powder.

(0337)

NMR spectrum (270 MHz, CD_3OD) δ ppm:2.35 (3H, s), 4.62 (2H, s), 8.76 (1H, s).

Reference Example 24

7- benzyl -1- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine.

Using the same procedures as in the method to synthesize 7- benzyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine, the title compound (1.7 g) was obtained as a yellow oily material from 4- (chloromethyl) imidazole hydrochloride (5.5 g, 3.3 x 10^{-2}mol).

(0338)

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:2.09 (3H, s), 2.80 (2H, t, J=5.3Hz), 3.59 (2H, s), 3.72 (2H, s), 3.99 (2H, t, J=5.3Hz), 7.30-7.40 (5H, m), 7.51 (1H, s).

Mass spectrum m/z:227 (M^+, C14H17N3)

Reference Example 25.

1- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine.

Palladium black (150 mg) and formic acid (200 μl) were added to methanol (4.5 ml) solution of 7- benzyl -1- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine (475 mg, 2.09 mmol) and the mixture was stirred at 50-70°C for five hours. The reaction liquid was filtered, and it was concentrated, and the title crude compound (300 mg) was obtained as yellow oily material.

(0339)

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:2.13 (3H, s), 3.19 (2H, t, J=5.3Hz), 3.72 (2H, s), 3.98 (2H, t, J=5.3Hz), 7.30-7.40 (5H, m), 7.42 (1H, s).

Reference Example 26

(2S, 4S)-4-(4- methoxybenzyl thio) -2-((1- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- yl) carbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine.

To dichloromethane (10 ml) suspension of (2S, 4S)- (4- methoxybenzyl thio) -1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2- carboxylic acid potassium salt (640 mg, 1.32 mmol), was added pivaloyl chloride (160 μl, 1.30 mmol)) at room temperature and the mixture was stirred for 1.2 hours. Triethylamine (180 μl, 1.29 mmol)) and crude 1- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine (about 1.3 mmol) were added to the reaction mixture liquid which had formed a solution and, the mixture was stirred for 30 minutes at the same temperature. On completion of the reaction, the solvent was eliminated by distillation, and the residue was dissolved in ethyl acetate, and it was washed with water. The organic layer was dried with anhydrous magnesium sulphate, and next the residue obtained by concentration was refined by column chromatography (development solvent :ethyl acetate -

methanol(1:0)-(9:1)) using alumina (30 g), and the title compound (150 mg) was obtained as a straw-coloured foamed substance.

(0340)

IR spectrum ν_{max} (CHCl3) cm^{-1}:2950,1700,1660,1605.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.75-2.00 (1H, m), 2.15 (3H, s), 2.45-2.60 (1H, m), 3.05-3.55 (2H, m), 3.72 (2H, s), 3.79 (3H, s), 3.65-4.20 (5H, m), 4.50-4.80 (3H, m), 4.90-5.25 (2H, m), 6.85 (2H, d, J=8.6Hz), 7.23 (2H, d, J=8.6Hz), 7.33 (1H, s), 7.45-7.50 (2H, m), 8.00-8.25 (2H, m).

Reference Example 27

2- (N-(tert-butoxycarbonyl) -N-((1- methyl -2- imidazolyl) methyl) amino) ethanol.

2- (chloromethyl) -1- methyl imidazole hydrochloride (9.3 g, 56 mmol) prepared by a method in accordance with Tokkai 63-255282 (bulletin 733 pages, lower left panel Example 3 and 4) and 2-aminoethanol (17.2 g, 281 mmol) were dissolved in acetonitrile (50 ml) - methanol (10 ml) mixed solvent and the mixture was stirred at 60°C for two hours. The solvent was eliminated under reduced pressure by distillation, and methanol (20 ml) and sodium hydroxide (4.5 g, 112 mmol) were added to the residue, and next, the mixture was heated under reduced pressure at 80°C, and the solvent and most of 2- aminoethanol were eliminated by distillation. Methanol (10 ml) and chloroform (40 ml) were added to the residue, and dissolution caused, and di (tert-butyl) dicarbonate (18.1 g, 83 mmol) was added and the mixture was stirred at 50°C for two hours.

After cooling, the mixture was diluted with chloroform, and was washed with water. The solvent was eliminated by distillation under reduced pressure, and the residue was subjected to flash column chromatography using silica gel 300 g, and it was eluted with ethyl acetate, and the colourless oily title compound (6.7 g, yield 47 %) was thereby obtained.

(0341)

IR spectrum ν_{max} (CHCl3) cm^{-1}:3150,3000,1680,1460,1400,1368,1170,1150.

NMR spectrum (60 MHz, $CDCl_3$) δ ppm:1.50 (9H, s), 3.3-4.0 (4H, m), 3.74 (3H, s), 4.47 (2H, s), 6.2 (1H, br), 6.80 (1H, brs), 6.93 (1H, brs).

Mass spectrum m/z:256 (M^++1), 225,199,182,169,155,137,124,110,96 (100 %), 57.

Reference Example 28.

2- (N-((1- methyl -2- imidazolyl) methyl) amino) ethanol • dihydrochloride.

Hydrochloric acid (4N- dioxane solution, 18 ml, 72 mmol) and methanol (20 ml) were added under ice cooling to 2- (N-(tert-butoxycarbonyl) -N-((1- methyl -2- imidazolyl) methyl) amino) ethanol (2.42 g, 9.44 mmol). The mixture was stirred at room temperature for one hour 30 minutes, and next, the solvent and excess hydrochloric acid were eliminated by distillation under reduced pressure, and the insoluble

powder obtained when ether and ethanol were added to the residue, was recovered by filtration, and the title compound which had melting point 173-176°C (2.05 g, yield 95 %) was obtained as a colourless powder.

(0342)

Elemental analysis values as C7H15Cl2N3O

Theoretical value C:36.86,H:6.63,N:18.42

Experimental value C:36.56,H:6.58,N:18.47

IR spectrum ν_{max} (KBr) cm^{-1}:3286,2995,2689,1603,1462,1329,1268,1090,999.

NMR spectrum (270 MHz, D2O) δ ppm:3.36 (2H, t, J=6Hz), 3.90 (2H, t, J=6Hz), 3.96 (3H, s), 4.73 (2H, s), 7.53 (1H, br.s), 7.54 (1H, br.s).

Mass spectrum m/z:156 (M^++1-2HCl), 137,124,110,95 (100 %).

Reference Example 29

(2S, 4S)-4- acetylthio -N- (2- hydroxyethyl) -N-((1- methyl -2- imidazolyl) methyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2- carboxamide.

(2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2- carboxylic acid potassium salt (563 mg, 1.38 mmol) was suspended in dichloromethane (4 ml), and pivaloyl chloride (167 mg, 1.38 mmol) was added under ice cooling and the mixture was stirred at room temperature for 30 minutes. Thereafter, a mixed suspension of 2-N-((1- methyl -2- imidazolyl) methyl) amino) ethanol dihydrochloride (317 mg, 1.39 mmol), triethylamine (500 mg, 4.94 mmol) and N,N-dimethylformamide (6 ml) was added under ice cooling to this. The mixture was stirred at room temperature for one hour, and next, it was diluted with ethyl acetate, and it was washed with dilute sodium carbonate solution. The solvent was eliminated by distillation under reduced pressure, and the residue was subjected to flash column chromatography using silica gel 10 g, and it was eluted with methanol - ethyl acetate (3:97), and pale yellow foamed title compound (406 mg, yield 58 %) was thereby obtained.

(0343)

IR spectrum ν_{max} (CHCl3) cm^{-1}:3150(br), 3000,1700,1660,1520,1345,1120.

NMR spectrum (60 MHz, $CDCl_3$) δ ppm:1.9-3.0 (2H, m), 2.30 (3H, s), 3.1-4.6 (13H, m), 4.6-5.3 (3H, m), 6.6-7.0 (2H, m), 7.2-7.7 (2H, m), 8.20 (2H, d, J=8Hz).

Mass spectrum m/z:368,326,233,198,124,96 (100 %).

Reference Example 30.

(1R, 5S, 6S) -2-(((2S,4S)-2- (N-(2- hydroxyethyl) -N-((1- methyl -2- imidazolyl) methyl) carbamoyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -4- yl) thio)-6-((R)-1- hydroxyethyl)-1- methyl carbapenem

-3- carboxylic acid 4- nitrobenzyl ester.

(2S, 4S)-2- acetylthio -N- (2- hydroxyethyl) -N-((1- methyl -2- imidazolyl) methyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2- carboxamide (518 mg, 1.03 mmol) was dissolved in methanol (3 ml), and a solution of sodium methoxide prepared using metallic sodium (26.4 mg, 1.15 mmol) and methanol (1 ml) was added under ice cooling. The mixture was stirred under ice cooling for 15 minutes, and next, acetic acid (69 mg, 1.15 mmol) was added, and a solution of (2S, 4S)-4- mercapto -2- (N-(2- hydroxyethyl) -N-((1- methyl -2- imidazolyl) methyl) carbamoyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine was obtained. Meanwhile, (1R, 3R, 5R, 6S) -6-((R)-1- hydroxyethyl)-1- methyl -2- oxo carba penam -3- carboxylic acid 4- nitrobenzyl ester (373 mg, 1.03 mmol) was dissolved in acetonitrile (5 ml), and diisopropyl ethylamine (146 mg, 1.13 mmol) and diphenyl chlorophosphate (304 mg, 1.13 mmol) were added under ice cooling and the mixture was stirred for 40 minutes. Next, to this, the solution of the above obtained (2S, 4S)-4- mercapto -2- (N-(2- hydroxyethyl) -N-((1- methyl -2- imidazolyl) methyl) carbamoyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine and diisopropyl ethylamine (146 mg, 1.13 mmol) were added. Furthermore the mixture was stirred under ice cooling for three hours, and next, dilute sodium carbonate solution was added, and the mixture was extracted with ethyl acetate. The extract was washed with saturated aqueous sodium chloride solution, and the solvent was eliminated by distillation under reduced pressure, and the residue was subjected to column chromatography using silica gel 15 g, and it was eluted with methanol - ethyl acetate (1:9), and the pale yellow foamed title compound (400 mg, yield 48 %) was thereby obtained.

(0344)

IR spectrum ν_{max} (CHCl3) cm^{-1}:3400,3000,1770,1705,1650,1520,1325.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.23 (3H, d, J=7Hz), 1.33 (3H, d, J=6Hz), 1.8-2.0 (1H, m), 2.7-2.9 (1H, m), 3.2-4.3 (13H, m), 3.66[3H X(1/2), s], 3.72[3H x (1/2), s], 4.1-4.3 (3H, m), 5.05[2H x (1/2), s], 5.18[2H x (1/2), s], 5.21 (1H, d, J=15Hz), 5.48 (1H, d, J=15Hz), 6.70 (1H, s), 6.78[1H x (1/2), s], 6.87[1H x (1/2), s], 7.38 (1H, d, J=9Hz), 7.48 (1H, d, J=9Hz), 7.63 (2H, d, J=9Hz), 8.14 (1H, d, J=9Hz), 8.18 (1H, d, J=9Hz), 8.22 (2H, d, J=9Hz).

Mass spectrum m/z:415,385,368,332,318,300 (100 %).

Reference Example 31.

(2- pyridyl) methyl aminoacetic acid ethyl ester

Bromoacetic acid ethyl ester (7.1 ml, 6.4X10-2mol)) was added under ice cooling slowly dropwise to benzene (35 ml) solution of 2- (aminomethyl) pyridine (7.0 g, 6.5 x 10^{-2}mol)) and the mixture was stirred at room temperature for 30 minutes. On completion of the reaction, the solvent was eliminated under reduced pressure by distillation, and the residue was dissolved in dichloromethane (150 ml), and it was washed with 2N-NaOH aqueous solution (50 ml). The organic phase was dried with anhydrous magnesium sulphate, and next the residue obtained by concentration was refined by column

chromatography (development solvent : ethyl acetate - dichloromethane (1:1) and then (ethylacetate - methanol(9:1))) using silica gel, and the title compound (4.24 g) was thereby obtained as a yellow oily material.

(0345)

IR spectrum ν_{max} (neat) cm^{-1}:3350,2990,1735,1590.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.28 (3H, t, J=7.3Hz), 2.16 (1H, br.s), 3.47 (2H, s), 3.95 (2H, s), 4.19 (2H, q, J=7.3Hz), 7.17 (1H, ddd, J=7.9, 4.7, 1.3Hz), 7.33 (1H, br.d, J=7.9Hz), 7.65 (1H, d, J=2.0, 7.9Hz), 8.55-8.59 (1H, m).

Reference Example 32.

N- (2- hydroxyethyl) -N-((2- pyridyl) methyl) amine.

To a suspension in tetrahydrofuran (40 ml) of lithium aluminum hydride (390 mg, 10.3 mmol), was slowly added a tetrahydrofuran (5 ml) solution of (2- pyridyl) methyl aminoacetic acid ethyl (2.00 g, 10.3 mmol) at room temperature and the mixture was stirred for 30 minutes. On completion of the reaction, 2N-NaOH aqueous solution (about 5 ml) was added and furthermore the mixture was stirred at room temperature for 30 minutes. The precipitated solid was separated by filtration, and the filtrate was concentrated, and the residue was refined using a Kugelrohr distillation apparatus, and the title compound (541 mg, about 180°C /10 mm Hg) was obtained as a straw-coloured oily substance.

(0346)

IR spectrum ν_{max} (neat) cm^{-1}:3275,2910,2850,1590,1570.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:2.87 (2H, t, J=5.3Hz), 3.0-3.3 (2H, brs), 3.67 (2H, t, J=5.3Hz), 7.20 (1H, dd, J=7.3, 4.0Hz), 7.24 (1H, d, J=7.3Hz), 7.66 (1H, dt, J=1.3, 7.3Hz), 8.56 (1H, brd, J=4.0Hz)

Reference Example 33.

(2S, 4S)-4- acetylthio -2- (N-(2- hydroxyethyl) -N-((2- pyridyl) methyl) carbamoyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine.

Pivaloyl chloride (251 μl, 2.04 mmol)) was added at room temperature to a dichloromethane (25 ml) suspension of (2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2- carboxylic acid potassium salt (830 mg, 2.04 mmol) and the mixture was stirred at the same temperature for 20 minutes. Thereto a dichloromethane (5 ml) solution of N- (2- hydroxyethyl) -N-((2- pyridyl) methyl) amine (330 mg, 2.50 mmol) was added and the mixture was stirred for 30 minutes. On completion of the reaction, the solvent was eliminated by distillation, and the residue was dissolved in ethyl acetate (100 ml), and the solution was washed respectively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution. The organic layer was dried with anhydrous magnesium sulphate,

and next, the residue which was obtained by elimination by distillation of the solvent was subjected to chromatography (developing solvent :ethyl acetate - methanol (98:2) using Lobar column B (made by Merck Co.), and the title compound (500 mg) was obtained as a straw-coloured foamed substance.

(0347)

IR spectrum ν_{max} (CHCl3) cm^{-1}:3200,3000,2930,2860,1695,1655.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.85-2.00 (1H, m), 2.29, 2.30, 2.31 (3H, sX3), 2.73, 2.98 (1H, dtX2,J=12.9, 7.6Hz), 3.38 (1H, t, J=9.8Hz), 3.45-3.60 (1H, m), 3.70-3.15 (5H, m), 4.16-4.65 (2H, m), 4.85-5.04 (2H, m), 5.15-5.30 (2H, m), 7.03, 7.20 (1H, ddX2,J=6.9, 5.4Hz), 7.29-7.51 (3H, m), 7.64-7.80 (1H, m), 8.08-8.25 (2H, m), 8.45, 8.57 (1H, brd, J=4.9Hz).

Reference Example 34

(1R, 5S, 6S) -6-((R)-1- hydroxyethyl)-2-(((2S,4S)-2- (N-(2- hydroxyethyl) -N-((2- pyridyl) methyl) carbamoyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -4- yl) thio)-1- methyl -1- carbapenem -3- carboxylic acid 4- nitrobenzyl ester.

[a] A methanol (0.25 ml) solution of sodium metal (23 mg, 1.0 mmol) was added at -78°C to methanol (15 ml) solution of (2S, 4S)-4- acetylthio -2- (N-(2- hydroxyethyl) -N-((2- pyridyl) methyl) carbamoyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine (500 mg, 9.95 x 10^{-4}mol)) and the mixture was stirred at room temperature for 15 minutes. On completion of the reaction, water (40 ml) and 0.5M phosphoric acid buffer (pH7, about 6 ml) were added, and next, the mixture was extracted with ethyl acetate, and the organic layer was dried with anhydrous magnesium sulphate. The solvent was eliminated by distillation, and the mercaptan was obtained.

(0348)

[b] Diphenylphosphoryl chloride (0.17 ml, 8.2 x 10^{-4}mol)) and diisopropyl ethylamine (143 μl, 8.2 x 10^{-4}mol)) were mixed under ice cooling with acetonitrile (10 ml) solution of (1R,3R,5R,6S)-6-((R)-1- hydroxyethyl)-1- methyl -2- oxo carba penam -3- carboxylic acid 4- nitrobenzyl ester (300 mg, 8.3X10-4mol)) and, for 30 minutes, the mixture was stirred at the same temperature. An acetonitrile (3 ml) solution of the mercaptan obtained in [a] and diisopropyl ethylamine (174 μl, 1.00 x 10^{-3}mol)) were added to reaction solution thereof and furthermore were stirred for six hours under ice cooling. On completion of the reaction, the solvent was eliminated by distillation, and it was diluted with ethyl acetate, and next, it was washed with sodium hydrogen carbonate aqueous solution. The organic layer was dried with anhydrous magnesium sulphate, and the residue obtained by elimination by distillation of the solvent was subjected to chromatography (development solvent :ethyl acetate - methanol (95:5) using a Lobar column B (made by Merck Co.), and the title compound (430 mg) was obtained as a straw-coloured foamed substance.

(0349)

IR spectrum ν_{max}(KBr) cm^{-1}:3414,2969,1771,1710,1655,1606..

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.26 (3H, d, J=7.3Hz), 1.36 (3H, d, J=6.4Hz), 1.85-2.05 (1H, m), 2.75-2.90 (1H, m), 3.26 (1H, br.d, J=6Hz), 3.30-4.05 (9H, m), 4.20-4.30 (2H, m), 4.45-4.69 (2H, m), 4.88-5.03 (2H, m), 5.19 (2H, s), 5.20-5.51 (2H, m), 7.08, 7.25 (1H, dd X2,J=6.8, 4.9Hz), 7.31-7.51 (3H, m), 7.61-7.77 (3H, m), 8.10-8.25 (4H, m), 8.45, 8.58 (1H, br.d, J=4.9Hz).

Reference Example 35

7- benzyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine.

To a tetrahydrofuran (10 ml) solution of 7- benzyl -3- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine (1.00 g, 4.69 mmol), a 1.5 M hexane solution (3.3 ml, 5.0 mmol) of n- butyllithium was added at -78°C, and the mixture was warmed to 0°C while stirring. Methyl iodide (2.1 g, 15 mmol) was added thereto at the same temperature and the mixture was stirred for 15 minutes. Sodium hydrogen carbonate aqueous solution was added to the reaction liquid and extraction carried out with ethyl acetate. The organic layer was dried with anhydrous magnesium sulphate, and was concentrated under reduced pressure. The residue was refined by column chromatography (development solvent :ethyl acetate - methanol(1:0)-(9:1)) using silica gel (20 g), and the title compound (930 mg) was obtained as a yellow oily material.

(0350)

IR spectrum ν_{max}(CHCl3) cm^{-1}:2950,2820,2760,1495.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:2.33 (3H, s), 2.86 (2H, t, J=5.9Hz), 3.64 (2H, s), 3.70 (2H, s), 3.86 (2H, t, J=5.9Hz), 6.62 (1H, s), 7.30-7.42 (5H, m).

Reference Example 36

3- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine • dihydrochloride.

Palladium black (600 mg) and formic acid (0.6 ml) were added to a methanol (20 ml) solution of 7- benzyl -3- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine (925 mg, 4.07 mmol) and the mixture was stirred at about 60°C for three hours. Water was added to the reaction liquid, and it was filtered, and next, it was concentrated, and it was dissolved in 1N- hydrogen chloride water and was stirred at 90°C for one hour. The reaction liquid was concentrated, and the title compound (900 mg) was obtained as pale yellow crystals (Mp. 215-220°C) by crystallization from ethanol - ethyl acetate.

(0351)

IR spectrum ν_{max}(KBr) cm^{-1}:3493,3362,3116,2994,2942,2902,2880,2750,2711.

NMR spectrum (270 MHz, D2O) δ ppm:2.37 (3H, s), 3.24 (2H, t, J=5.6Hz), 3.81 (2H, t, J=5.6Hz), 4.03 (2H, s), 6.70 (1H, s).

Reference Example 37

(2S, 4S)-4- acetylthio -2-(3- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl)-1-(4- nitrobenzyl oxycarbonyl) pyrrolidine.

Pivaloyl chloride (406 µl, 3.30 mmol)) was added to dichloromethane (20 ml) suspension of ((2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2- carboxylic acid potassium salt (1.34 g, 3.30 mmol) at room temperature and the mixture was stirred for 15 minutes. Next, triethylamine (1.4 ml, 10 mmol) and 3- methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine dihydrochloride (630 mg, 3.00 mmol) were added at room temperature and the mixture was stirred for 30 minutes. The reaction liquid was diluted with ethyl acetate (100 ml), and was washed twice with water (50 ml) and was washed with saturated aqueous sodium chloride solution (50 ml). The organic layer was dried with anhydrous magnesium sulphate, and, after concentration, the residue was refined using a short column (development solvent :ethyl acetate - methanol (95:5)) with alumina, and the title compound (1.16 g) was obtained as a straw-coloured foamed substance.

(0352)

IR spectrum ν_{max} (KBr) cm^{-1}:2947,1710,1660,1607,1522.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.80-2.00 (1H, m), 2.25, 2.35 (3H, s X2), 2.34 (3H, s), 2.68-2.88 (1H, m), 3.46 (1H, br.t, J=9.6Hz), 3.60-4.30 (4H, m), 4.60-4.90 (4H, m), 4.90-5.30 (2H, m), 6.75, 6.90 (1H, sX2), 7.34, 7.51 (2H, d X2,J=8.6Hz), 8.13, 8.22 (2H, dX2,J=8.6Hz).

Reference Example 38

7- benzyl -3- formyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine.

A 1.5 M hexane solution (5.0 ml, 7.5 mmol) of n- butyllithium was added at -78°C to a tetrahydrofuran (10 ml) solution of 7- benzyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine (1.45 g, 6.80 mmol) and the mixture was warmed to 0°C and was stirred for ten minutes. The mixture was cooled to -78°C again, and dimethylformamide (731 mg) was added, and then warmed to 0°C and furthermore was stirred for ten minutes. Saturated aqueous sodium bicarbonate solution (20 ml) and water (50 ml) were added to the reaction mixture liquid and thereafter extraction with ethyl acetate (50 ml) was carried out. The organic layer was washed with water twice and saturated aqueous sodium chloride solution (20 ml). The organic layer which was dried on anhydrous magnesium sulphate was subjected without further treatment to short column (development solvent : ethyl acetate) using silica gel and was refined, and the title compound (1.45 g) was obtained as a straw-coloured oily substance.

(0353)

IR spectrum ν_{max} (CHCl3) cm^{-1}:2980,2805,2750,1675.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:2.88 (2H, t, J=5.6Hz), 3.72 (4H, s), 4.44 (2H, t, J=5.6Hz),

7.02 (1H, s), 7.28-7.43 (5H, m), 9.73 (1H, s).

Reference Example 39

7- benzyl -3- (hydroxymethyl) -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine.

Sodium borohydride (150 mg) was added at room temperature to a methanol (15 ml) solution of 7-benzyl -3- formyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine (900 mg, 3.73 mmol) and the mixture was stirred for one hour. Saturated aqueous sodium bicarbonate solution (30 ml) and water (30 ml) were added to the reaction mixture liquid, and extraction was carried out three times with ethyl acetate. The organic layer which was dried with anhydrous magnesium sulphate was concentrated, and the title crude compound (900 mg) was obtained as a colourless oily substance.

(0354)

IR spectrum ν_{max} (CHCl3) cm^{-1}:3140,2980,2950,2810,2750.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:2.89 (2H, t, J=5.9Hz), 3.64 (2H, s), 3.70 (2H, s), 4.09 (2H, t, J=5.9Hz), 4.60 (2H, s), 7.30-7.40 (5H, m).

Reference Example 40

3- (hydroxymethyl) -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine • dihydrochloride

Palladium black (400 mg) and formic acid (500 μl) were added to methanol (10 ml) solution of 7-benzyl -3- (hydroxymethyl) -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine (1.10 g, 4.52 mmol) and the mixture was stirred at about 70°C for three hours. On completion of the reaction, water (about 15 ml) was added, and filtration was carried out. The filtrate was concentrated, and the residue was dissolved in 1N-HCl aqueous solution and was stirred at about 80°C for one hour. The reaction mixture liquid was concentrated without further treatment and was crystallised from methanol - isopropyl alcohol. The title compound (720 mg) was obtained as colourless acicular crystals (Mp.198-199°C).

(0355)

IR spectrum ν_{max} (KBr) cm^{-1}:3467,3413,3109,3063,2963,2804,1620,1560.

NMR spectrum (270 MHz, D2O) δ ppm:3.82 (2H, t, J=5.9Hz), 4.51 (2H, t, J=5.9Hz), 4.60 (2H, d, J=1.5Hz), 4.94 (2H, s), 7.44 (1H, t, J=1.5Hz).

Reference Example 41

7- (tert butoxycarbonyl) -3-(4- nitrobenzyl oxycarbonyl oxy) methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine.

A methanol (3 ml) solution of di (tert-butyl) di carbonate (500 g, 2.29 mmol) was added at room temperature to a methanol (10 ml) suspension of 3- (hydroxymethyl) -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine dihydrochloride (480 mg, 1.97 mmol) and potassium carbonate (140 mg, 1.01 mmol).

Triethylamine (280 μl, 2.01 mmol)) was added thereto and the mixture was stirred at room temperature for one hour. The reaction mixture was washed with hexane, and the methanol layer was concentrated, and it was diluted with ethyl acetate. This suspension was washed with saturated aqueous sodium bicarbonate solution. The solid obtained by concentrating the organic layer which had been dried with anhydrous magnesium sulphate was washed with hexane. This solid was dissolved in dichloromethane (10 ml). Thereto dimethylaminopyridine (250 mg, 2.05 mmol) and 4- nitrobenzyl oxycarbonyl chloride (440 mg, 2.04 mmol) were added at room temperature and the mixture was stirred for 30 minutes. The reaction liquid was concentrated, and it was diluted with ethyl acetate, and it was washed with sodium hydrogen carbonate aqueous solution, water and aqueous sodium chloride. The organic layer which was dried on anhydrous magnesium sulphate was concentrated and the residue was subjected to silica gel column chromatography (development solvent : ethyl acetate) and was thereby refined, and the title compound (656 mg) was obtained as a colourless oily substance.

(0356)

IR spectrum ν_{max} (CHCl3) cm^{-1}:2970,1750,1690,1605..

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.49 (9H, s), 3.85 (2H, brt, J=5.3Hz), 4.09 (2H, t, J=5.3Hz), 4.67 (2H, s), 5.27 (2H, s), 5.33 (2H, s), 6.95 (1H, s), 7.54 (2H, d, J=8.7Hz), 8.24 (2H, d, J=8.7Hz).

Reference Example 42

3-(4- nitrobenzyl oxycarbonyl oxy) methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine • dihydrochloride.

7- (tert-butoxycarbonyl) -3-(4- nitrobenzyl oxycarbonyl oxy) methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine (1.3 g, 3.0 mmol) was dissolved in ethyl acetate (3 ml), and 4N hydrogen chloride - dioxane solution 20 ml were added thereto and the mixture vigorously stirred at room temperature for three hours. The precipitated white solid was recovered by filtration, and was washed with ethyl acetate, and the title compound 1.10 g was obtained as crude crystals (Mp155-157°C).

(0357)

IR spectrum ν_{max} (KBr) cm^{-1}:3093,3059,2978,2950,2913,2774,2478,2441,2394,1746,1617,1606.

NMR spectrum (270 MHz, D2O) δ ppm:3.86 (2H, t, J=5.9Hz), 4.64 (2H, t, J=5.9Hz), 4.65 (2H, s), 5.37 (2H, s), 5.54 (2H, s), 7.56 (1H, s), 7.64 (2H, d, J=8.8Hz), 8.27 (2H, d, J=8.8Hz).

Reference Example 43

(2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) -2-(3- (4- nitrobenzyl oxycarbonyl oxy) methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine.

The title compound (1.18 g) was obtained as a straw-coloured foamed substance using 3-(4- nitrobenzyl oxycarbonyl oxy) methyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine dihydrochloride (810 mg)

using the same procedures used in the synthesis of Reference Example 22 for ((2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl)-2- (5,6,7,8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine.

(0358)

IR spectrum ν_{max} (KBr) cm^{-1}:3113,3081,2953,2872,1752,1710,1663,1608.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.85-2.05 (1H, m), 2.34 (3H, s), 2.67-2.90 (1H, m), 3.46 (1H, br.t, J=8Hz), 3.80-4.40 (6H, m), 4.65-5.05 (3H, m), 5.15-5.40 (6H, m), 6.95, 6.99 (1H, sX2), 7.30-7.56 (4H, m), 8.00-8.25 (4H, m).

Reference Example 44

3- azide -7- benzyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine.

To a tetrahydrofuran (20 ml) solution of 7- benzyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine (2.00 g, 9.38 mmol), a 1.5 M hexane solution (6.7 ml, 10 mmol) of n- butyllithium was added at -78°C and the mixture stirred. The mixture was stirred at the same temperature for five minutes and next, p-toluenesulphonylazide (1.97 g, 10.0 mmol) was added and the mixture stirred for a further ten minutes. A saturated aqueous sodium bicarbonate solution (20 ml) was added to the reaction liquid, and next, water (30 ml) was added and extraction was carried out twice with ethyl acetate (100 ml, 20 ml). The combined organic layers were extracted with 2N- hydrochloric acid (100 ml). The aqueous layer was adjusted to about pH12 with 2N- sodium hydroxide aqueous solution, and extracted three times with ethyl acetate (100 ml). The combined organic layers were dried on anhydrous magnesium sulphate, and concentrated under reduced pressure. The title compound (2.11 g) was obtained as a pale orange oily substance by subjecting the obtained residue to column chromatography (development solvent : ethyl acetate) using silica gel (10 g) and thereby carrying out purification.

IR spectrum ν_{max} (CHCl3) cm^{-1}:2965,2800,2760,2150.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:2.79 (2H, t, J=5.6Hz), 3.59 (2H, s), 3.67 (2H, s), 3.72 (2H, t, J=5.6Hz), 6.57 (1H, s), 7.19-7.43 (5H, m).

Reference Example 45

3- amino -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine • dihydrochloride.

Palladium black (100 mg) and formic acid (300 μl) were added to methanol (15 ml) solution of 3- azide -7- benzyl -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine (2.05 g, 8.54 mmol) and the mixture was stirred at room temperature for ten minutes. When the vigorous effervescence had ceased, the reaction mixture liquid was heated to about 70°C and furthermore palladium black (700 mg) and formic acid (1.5 ml) were added and the mixture was stirred for eight hours. The reaction liquid was filtered after dilution with water (10 ml). The filtrate was concentrated and thereafter dissolved in 1N- hydrochloric acid (30 ml) and the solution was heated at 80-90°C for one hour. The reaction liquid was concentrated

without further treatment, and was crystallised from methanol - diisopropyl ether, and the title compound (1.52 g) was obtained as colourless acicular crystals (Mp. 238°C).

(0359)

IR spectrum ν_{max} (KBr) cm^{-1}:3260,3208,3120,2995,2774,1667.

NMR spectrum (270 MHz, D2O) δ ppm:3.73 (2H, t, J=6.1Hz), 4.11 (2H, t, J=6.1Hz), 4.40 (2H, d, J=1.4Hz), 6.84 (1H, t, J=1.4Hz).

Reference Example 46

7- (tert-butyloxycarbonyl) -3-(4- nitrobenzyl oxycarbonyl) amino -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine.

Toluethylamine (1.05 ml, 7.50 mmol) and di (tert-butyl) di carbonate (1.5 g, 6.9 mmol) were added to a methanol (15 ml) suspension of 3- amino -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine dihydrochloride (820 mg, 3.58 mmol) and the mixture was stirred at room temperature for one hour. On completion of the reaction, the mixture was concentrated under reduced pressure, diluted with ethyl acetate (100 ml), and next washed with water (50 ml). The organic layer which was dried on anhydrous magnesium sulphate was concentrated under reduced pressure, and the residue was washed with hexane. The obtained solid was dissolved in dichloromethane (15 ml), and thereto dimethylaminopyridine (860 mg) and 4- nitrobenzyl oxycarbonyl chloride (1.13 g) were added and the mixture was stirred at room temperature for 20 hours. The reaction liquid was diluted with ethyl acetate (150 ml) and was washed with water (100 ml). The organic layer was dried with anhydrous magnesium sulphate, and was concentrated under reduced pressure and the obtained residue was subjected to column chromatography (development solvent :ethyl acetate - methanol:(1:0)-(9:1)), using silica gel (20 g) and thus refined, and the title compound (1.17 g) was obtained as a pale yellow substance.

IR spectrum ν_{max} (CHCl3) cm^{-1}:3370,2980,1720,1685,1595..

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.49 (9H, s), 3.71 (2H, t, J=6.1Hz), 3.88 (2H, t, J=6.1Hz), 4.55 (2H, s), 6.45 (1H, s), 7.58 (2H, d, J=8.6Hz), 7.20 (2H, d, J=8.6Hz).

Reference Example 47

3-(4- nitrobenzyl oxycarbonyl) amino -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine • dihydrochloride.

7- (tert-butoxycarbonyl) -3-(4- nitrobenzyl oxycarbonyl) amino -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine (1.15 g, 2.76 mmol) was suspended in ethyl acetate (15 ml), and 4N- hydrogen chloride - ethyl acetate solution (10 ml) was added and the mixture was stirred at room temperature for four hours. The precipitated white solid was recovered by filtration and was washed with ethyl acetate, ether. It was dried under reduced pressure, and the title compound (903 mg) was obtained as powdered crystals (Mp180-185°C).

(0360)

IR spectrum ν_{max} (KBr) cm^{-1}:3380,3210,3143,2923,2782,1744,1668,1631.
NMR spectrum (270 MHz, D2O) δ ppm:3.82 (2H, t, J=5.9Hz), 4.36 (2H, t, J=5.9Hz), 4.57 (2H, s), 5.46 (2H, s), 7.24 (1H, s), 7.67 (2H, d, J=8.8Hz), 8.29 (2H, d, J=8.8Hz).

Reference Example 48

(2S, 4S) -4- acetylthio -1- methyl -2-(3- (4- nitrobenzyl oxycarbonyl) amino -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine -7- ylcarbonyl) pyrrolidine

To dichloromethane (15 ml) suspension of (2S, 4S)-4- acetylthio -1- methylpyrrolidine -2- carboxylic acid potassium salt (618 mg, 2.56 mmol), pivaloyl chloride (315 μl, 2.56 mmol)) was added at room temperature and the mixture was stirred for 30 minutes. Triethylamine (1.1 ml, 7.7 mmol) and 3-(4- nitrobenzyl oxycarbonyl) amino -5, 6, 7, 8- tetrahydroimidazo (1, 5-a) pyrazine dihydrochloride (1.00 g, 2.56 mmol) were added to the reaction mixture liquid and the mixture was stirred at the same temperature for 12 hours. The reaction liquid was concentrated under reduced pressure to about half, and it was diluted with ethyl acetate (150 ml), and it was washed respectively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution. The organic layer which was dried on anhydrous magnesium sulphate was concentrated under reduced pressure and the residue was subjected to column chromatography (development solvent :ethyl acetate - methanol(9:1) then (7:3)) using silica gel (20 g) and was thereby refined. The title compound (879 mg) was thereby obtained as a yellow foamed substance.

(0361)

IR spectrum ν_{max} (KBr) cm^{-1}:3344,2947,2849,2787,1733,1686,1637,1590,1520.
NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.78-1.95 (1H, m), 2.32 (3H, s), 2.35 (3H, brs), 2.70-2.85 (2H, m), 2.90 (1H, br.s), 3.07 (1H, dd, J=10.7, 2.4Hz), 3.22-3.30 (1H, m), 3.70-4.25 (5H, m), 4.65 (2H, br.s), 4.75 (2H, s), 6.49 (1H, br.s), 7.58 (2H, d, J=8.6Hz), 8.20 (2H, d, J=8.6Hz).

Reference Example 49

4,5,6,7- tetrahydroimidazo (4,5-c) pyridine • dihydrochloride.

Histamine dihydrochloride (1.0 g, 5.3 mmol) was dissolved in concentrated hydrochloric acid (11 ml), and dimethoxymethane (1.6 ml) was added, and the mixture was refluxed for 24 hours. The reaction liquid was concentrated without further treatment, and next, was crystallised from methanol - isopropyl alcohol, and the title compound (650 mg) was obtained as powdered crystals (Mp. 210°C).

(0362)

IR spectrum ν_{max} (KBr) cm^{-1}:3455,3330,3102,2995,2924,2704,2611,2453,1654.
NMR spectrum (270 MHz, D2O) δ ppm:3.20, 3.27 (2H, t X2,J=6.2Hz), 3.74 (2H, t, J=6.2Hz), 4.55 (2H, s), 8.78 (1H, brs).

Reference 50

Tert - butyl N- (2- hydroxyethyl) -N- propargyl carbamate.

Ethanolamine (7.7 g, 1.3 X10-1mol)) was dissolved in tetrahydrofuran - dimethylformamide (1:1) mixed solvent (50 ml), and next, tetrahydrofuran (10 ml) solution of propargyl bromide (3.0 g, 2.5 X10-2mol)) was added dropwise at room temperature over a period of ten minutes while stirring. The mixture was stirred for a further 30 minutes, and next, it was left to stand at room temperature overnight. The reaction mixture liquid was concentrated under reduced pressure at 50°C, and the residue (7.5 g) was obtained. This was dissolved in dichloromethane (50 ml), and di (tert-butoxy) dicarbonate (15 g) and triethylamine (4.5 ml) were added and the mixture was stirred at room temperature for three hours. On completion of the reaction, the mixture was diluted with ethyl acetate (300 ml) and was washed with saturated aqueous sodium bicarbonate solution (150 ml). The aqueous phase was extracted with ethyl acetate (100 ml), and next the combined organic phase was dried with anhydrous magnesium sulphate, and was concentrated, and the obtained residue was refined by column chromatography (development solvent : hexane - ethyl acetate (2:1) and then, ethyl acetate) using silica gel (about 300 g), and the title compound (2.57 g) was thereby obtained as a colourless oily substance.

(0363)

IR spectrum ν_{max} (neat) cm^{-1}:3450,3300,2975,2930,2121,1680.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.48 (9H, s), 2.25 (1H, t, J=2.0Hz), 2.80 (1H, br.s), 3.51 (2H, t, J=5.3Hz), 3.80 (2H, q, J=5.3Hz), 4.09 (2H, br.s).

Reference Example 51

(1,2,3) - triazolo (1, 5-a)-5, 6, 7, 8- tetrahydro pyrazine • dihydrochloride.

To tetrahydrofuran solution (20 ml) of tert - butyl N- (2- hydroxyethyl) -N- propargyl carbamate (1.30 g, 6.52 mmol) and triphenylphosphine (1.73 g, 6.60 mmol), diethyl azodicarboxylate ester (1.04 ml, 6.60 mmol) was added at room temperature and the mixture was stirred for five minutes. Thereafter tetrahydrofuran solution (7 ml) of diphenylphosphoryl azide (1.42 ml, 6.60 mmol) was added slowly dropwise at room temperature over a period of five minutes and the mixture was stirred for 22 hours. On completion of the reaction, the solvent was eliminated by distillation, and dilution carried out with ethyl acetate (200 ml), and the mixture was washed with water (100 ml) and saturated aqueous sodium chloride solution (100 ml). The organic layer was dried with anhydrous magnesium sulphate, and next was concentrated. The obtained residue was dissolved in toluene (40 ml) and was heated under reflux for one hour. On completion of the reaction, the solvent was eliminated by distillation, and the residue was subjected to column chromatography (development solvent : ethyl acetate - hexane (1:1)) using silica gel (40 g), and high polarity impurities were thereby eliminated. All the fractions which contained the target substance were combined, and concentrated, and the obtained residue was dissolved in ethyl

acetate (30 ml), and thereto 4N-HCl - dioxane solution (20 ml) was added under ice cooling and the mixture was stirred at room temperature for one hour. On completion of the reaction, the precipitated white solid was recovered by filtration, and was washed with ethyl acetate, and the title compound (360 mg) was thereby obtained as white crystals (Mp.170°C).

(0364)

IR spectrum ν_{max} (KBr) cm^{-1}:3305,3106,2983,2933,2796,2700,2646,1982,1598,1588,1552.
NMR spectrum (270 MHz, CD_3OD) δ ppm:3.87 (2H, t, J=5.9Hz), 4.67 (2H, s), 4.78 (2H, t, J=5.9Hz), 7.88 (1H, s).

Reference Example 52

(2S, 4S)-4- acetylthio -2-((1, 2, 3) - triazolo (1, 5-a)-5, 6, 7, 8- tetrahydro pyrazine -7 ylcarbonyl)-1-(4-nitrobenzyl oxycarbonyl) pyrrolidine.

Pivaloyl chloride (606 µl, 4.92 mmol)) was added at room temperature to a dichloromethane (50 ml) suspension of (2S, 4S)-4- acetylthio -1-(4- nitrobenzyl oxycarbonyl) pyrrolidine -2- carboxylic acid potassium salt (2.00 g, 4.92 mmol) and the mixture was stirred for 30 minutes. Thereto triethylamine (2.09 ml, 15.0 mmol) and (1,2,3) triazolo (1, 5-a)-5, 6, 7, 8- tetrahydro pyrazine dihydrochloride (960 mg, 5.00 mmol) were added and the mixture was stirred at room temperature for one hour. On completion of the reaction, the mixture was diluted with ethyl acetate (about 300 ml) and was washed with 0.1 M phosphoric acid buffer (pH7.4,150ml), and the organic layer was dried with anhydrous magnesium sulphate. The obtained residue was refined by column chromatography (development solvent : ethyl acetate-methanol (95:5)) using silica gel (20 g), and, after concentration, the title compound (1.16 g) was obtained as a straw-coloured foamed substance.

(0365)

IR spectrum ν_{max} (KBr) cm^{-1}:2948,1709,1665,1607,1522..
NMR spectrum (270 MHz, $CDCl_3$) δ ppm :1.85-2.10 (1H, m), 2.65-2.90 (1H, m), 2.34 (3H, s), 3.46 (1H, dd, J :10.3, 9.3 Hz), 3.90-4.05 (2H, m), 4.08-5.10 (7H, m), 5.19 (2H, s), 7.49 (2H, d, J :8.8 Hz), 7.58 (1H, s), 8.22 (2H, d, J :8.8 Hz).

Reference Example 53

7- (t- butoxycarbonyl) -5, 6, 7, 8- tetrahydro tetrazolo (1, 5-a) pyrazine.

4- (tert butoxycarbonyl) -2- piperazinone (1.00 g, 5.0 mmol) and 2,6- dimethylpyridine (1.14 g, 10.6 mmol) was dissolved in dichloromethane (12 ml), and anhydrous trifluoromethanesulfonic acid (1.51 g, 5.3 mmol) was added at -78°C. 20 minutes later, a mixture of azidotrimethylsilane (1.61 g, 14.0 mmol) and 1N- fluorinated tetrabutyl ammonium - tetrahydrofuran solution (14.0 ml, 14.0 mmol) was added at the same temperature. The reaction liquid was stirred for two hours while ice-cold, and next, dilute

sodium bicarbonate solution was added, and the mixture was extracted with chloroform. The solvent was eliminated by distillation under reduced pressure, and the residue was subjected to column chromatography using silica gel 100 g, and it was eluted with ethyl acetate - hexane (2:3), and the solid title compound (920 mg, yield 81 %) was thereby obtained. The solid was recrystallised from ethyl acetate - hexane, and a pure product of colourless acicular crystals which had melting point 95-97°C was obtained.

(0366)

Elemental analysis values as C19H15N5O2.

Theoretical value C:47.99,H:6.71,N:31.09 experimental value C:47.90,H:6.83,N:30.87

IR spectrum ν_{max} (KBr) cm^{-1}:2984,1700,1419,1245,1236,1167.

NMR spectrum (270 MHz, $CDCl_3$) δ ppm:1.50 (9H, s), 3.97 (2H, t, J=6Hz), 4.45 (2H, t, J=6Hz), 4.95 (2H, s).

Mass spectrum m/z:226 (M^++1), 210,152,125,57 (100 %).

Reference Example 54

5,6,7,8- tetrahydro tetrazolo (1, 5-a) pyrazine • hydrochloride.

Hydrochloric acid (4N dioxane solution, 10 ml, 40 mmol)) was added under ice cooling to 7- (tert-butoxycarbonyl) -5, 6, 7, 8- tetrahydro tetrazolo (1, 5-a) pyrazine (887 mg, 3.94 mmol) and the mixture was cooled with ice and was stirred for two hours 30 minutes. The solvent was eliminated by distillation under reduced pressure, and ethyl ether was added to the residue, and the insolubles were recovered by filtration, and the title compound comprising a colourless powder of melting point 92-92.5°C (336 mg, yield 53 %) was thereby obtained.

(0367)

IR spectrum ν_{max} (KBr) cm^{-1}:3536,2686,1348.

NMR spectrum (270 MHz, CD_3OD) δ :3.85 (2H, t, J=6Hz), 4.80-4.90 (4H, m).

Mass spectrum m/z:125 (M^+-HCl), 69, 57 (100 %), 42.

Formulation Example 1

Hard capsule agent

The compound of Example 1 in powdered form 100 mg, lactose 150 mg, cellulose 50 mg and magnesium stearate 6 mg were each packed into a normal two part type hard gelatin capsule, and a unit capsule was thereby produced, and it was washed and thereafter dried.

(0368)

Formulation Example 2

Soft capsule agent

A mixture of the compound of Example 1 was prepared in a digestible oily substance, such as for example soya bean oil, cottonseed oil or olive oil, and the mixture was injected into gelatin with original substitution pump, and soft capsule containing active ingredient 100 mg was thereby obtained, and thereafter washing and drying were carried out.

(0369)

Formulation Example 3

Tablets

In accordance with normal methods a tablet was produced using the compound of Example 1 100 mg, colloidal silicon dioxide 0.2 mg, magnesium stearate 5 mg, microcrystalline cellulose 275 mg, starch 11 mg and lactose 98.8 mg.

(0370)

Moreover, a coating agent was applied as desired.

(0371)

Formulation Example 4.

Injection

In the production, the compound of Example 1 in an amount of 1.5 wt.% was stirred in propylene glycol in an amount of 10vol.%, and thereafter this was made up to a fixed volume with water used for injection, and thereafter sterilization carried out.

(0372)

Formulation Example 5

Suspension agent

A 5 ml volume was produced containing the finely-powdered compound of Example 1, 100 mg, sodium carboxymethyl cellulose, 100 mg, sodium benzoate, 5 mg, sorbitol solution (Pharmacopeia of Japan), 1.0 g, and vanillin, 0.025 ml.

Rising Sun Communications Ltd. Terms and Conditions (Abbreviated)

Rising Sun Communications Ltd. shall not in any circumstances be liable or responsible for the accuracy or completeness of any translation or unwritten or written opinion unless such an undertaking has been given and authorised by Rising Sun Communications Ltd. in writing beforehand. More particularly, Rising Sun Communications Ltd. shall not in any circumstances be liable for any direct, indirect, consequential or financial loss or loss of profit resulting directly or indirectly from the use of any translation or consultation services by the customer.

Rising Sun Communications Ltd. retains the copyright to all of its' translation products unless expressly agreed in writing to the contrary. The original buyer is permitted to reproduce copies of a translation for their own corporate use at the site of purchase, or directly for their own patent filing purposes, or in the case of a firm of Patent Attorneys, for their Client's patent filing purposes, however publication in written or electronic format for resale or other dissemination to other wider audiences is strictly forbidden unless by prior written agreement.

The Full Terms and Conditions of Business of Rising Sun Communications may be found at the web site address <http://www.risingsun.co.uk/Terms_of_business.html>